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Differential Regulation of Th1/Th2 Cytokine Responses by Placental Protein 14

Galit Mishan-Eisenberg,⁎ Zipora Borovsky, ⁎ Matthew C. Weber, † Roi Gazit, ‡ Mark L. Tykocinski, † and Jacob Rachmilewitz*✉


Naive CD4+ T cells can differentiate into distinct effector cell subsets, characterized by the production of cytokines that promote different types of immune responses. Th1 cells express the hallmark cytokines IL-2 and IFN-γ, which are linked to cell-mediated immunity, whereas Th2 cells predominantly express IL-4 and IL-5 and promote humoral immunity. The selective differentiation of either subset is established during priming and can be significantly influenced by a variety of factors. One of these factors, the cytokine environment, has been presented as the major factor influencing T help development. Hence, during in vitro activation, polarization of naive T cells can be driven to the Th1 or Th2 phenotype by the addition of IL-12 or IL-4, respectively, in conjunction with blocking Abs to the cytokine that drives the alternate phenotype. In addition, the potency of TCR signaling that depends on priming conditions such as the nature (i.e., agonist or altered peptide ligand) and dose of Ag as well as the presence of costimulation also contributes to Th1 vs Th2 phenotype choice. The costimulatory receptor, CD28, by triggering an active accumulation of various cell surface molecules to the interface of the T cell and the APC, contributes to signal strength and increases the amplitude and duration of TCR signaling.

In contrast to the amplifying effects of costimulation, we have previously demonstrated that the immunomodulatory glycoprotein, placental protein 14 (PP14), also known as glycodelin (4)), translocates to APC:T cell contact sites, where it decreases stability of TCR-induced phosphoproteins (5). This latter activity of PP14 fits in well with the antagonism between CD28-mediated costimulation and PP14-mediated inhibition (6) as well as with recent data indicating that the inhibitory activity of PP14 is mediated by the tyrosine phosphatase receptor, CD45 (7). These findings help to explain the capacity of PP14 to desensitize TCR signaling and to operate via a unique immunoregulatory mechanism, rheostatically elevating TCR activation thresholds.

PP14 has other described activities outside the immune system, including the ability to inhibit sperm–zona interaction (8, 9), to promote angiogenesis, possibly by promoting vascular endothelial growth factor expression (10). However, the immunoinhibitory functions attributed to PP14 are of special interest in light of its tissue distribution. PP14 is expressed in maternal reproductive tracts and is highly abundant during early pregnancy, constituting up to 10% of total decidual protein in the first trimester, and occurs in remarkably high concentrations in amniotic fluid (AF) during the first half of pregnancy (125 mg/L; of decidual origin) (11, 12). Significant concentrations of PP14 are also present in tumors of reproductive organs (13, 14), in plasma during early pregnancy (12), and in male seminal fluid (15). Interestingly, decidual NK cells were shown to express PP14 (16), and in turn PP14 has been shown to suppress NK function (17). PP14 has also been identified outside of the reproductive system, within cells of the megakaryocytic lineage and platelets (18). Taken together, these findings may explain, at least in part, the correlation between PP14 serum levels and the establishment and progression of a normal pregnancy (19–21), and it is thus tempting to speculate that PP14 may contribute to maternal immunotolerance to the semiallogeneic embryo.

Based on our previous studies demonstrating the ability of PP14 to desensitize TCR signaling, we have now looked for differential effects by PP14 on Th1 vs Th2 responses during T cell priming. Our data demonstrated that whereas both Th1 and Th2 responses were inhibited by PP14, Th1 responses were overall more sensitive to inhibition. Mechanistically, PP14-treated cells showed impaired TCR-induced repression of the Th2-linked transcription factor, GATA-3. The data suggest that PP14 may preferentially antagonize Th1 commitment, hence skewing the response toward the Th2 phenotype.

Materials and Methods

Cells

Cells were purified from the venous blood of healthy donors. CD4+ T cells were isolated either by positive selection using anti-CD4 microbeads with

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Abbreviations used in this paper: PP14, placental protein 14; AF, amniotic fluid; SEB, staphylococcal enterotoxin B.
magnetic cell isolation system (Miltenyi Biotec, Bergisch Gladbach, Germany), or by negative selection using RosetteSep human CD4+ T cell enrichment mixture (StemCell Technologies, Vancouver, Canada). All of the experiments were performed with CD4+ T cells isolated by one of the two methods, achieving similar results. As a source of APC, monocytes were isolated from PBMC populations by either adherence to plastic, as previously described (6), or RosetteSep human CD4+ T cell enrichment mixture (StemCell Technologies). The cells were maintained in RPMI 1640 medium (Biological Industries, Beit-Haemek, Israel) supplemented with 10% heat-inactivated FCS (Biological Industries), 2 mM glutamine, and penicillin/streptomycin.

Monocytes were washed with medium and resuspended at 1 × 10^6 cells/ml before being loaded with the superantigen staphylococcal enterotoxin B (SEB) at the indicated concentrations for 2 h at 4°C. The SEB-loaded cells were then washed three times with medium and diluted to 1 × 10^6 cells/ml in medium before adding them to culture.

**AF samples, PP14 immunoadsorption, and production of PP14•Fcγy**

Discarded human AF samples were obtained from the Center for Human Genetics Laboratory at Hadassah Hospital and stored at -80°C. Samples obtained from several patients (collected at 16–18 wk of gestation) were pooled and filtered sterilized before use. Anti-PP14 polyclonal Ab (Ab) (18) were coupled to protein A-Sepharose beads (Sigma-Aldrich, St. Louis, MO) to generate an immunoadsorbent. Immunoadsorption was conducted as described (22). PP14•Fcγy was prepared, as described (7), and each fraction preparation was tested for activity before subsequent use in experiments.

**Cytokine production**

Cultures containing 10^6 CD4+ T cells and 10^6 monocytes loaded with various concentrations of the superantigen SEB, in the absence or presence of either AF or PP14•Fcγy, were plated in 1 ml of RPMI 1640 containing 10% FCS in individual wells of a 24-well culture plate. Cells were stimulated for the indicated times, and conditioned medium was collected. IL-2, IL-4, IL-5, IL-13, and IFN-γ levels in the conditioned medium were assayed by ELISA (R&D Systems, Minneapolis, MN).

**Flow cytometry of cell surface markers**

CD4+ T cells were cultured with SEB-loaded monocytes for 48 h in the absence or presence of either AF or PP14•Fcγy, CXCR4, CXCR3, and GM1 expression was measured by direct immunofluorescence using PE-conjugated anti-CXCR4 mAb, FITC-conjugated anti-CXCR3 mAb (R&D Systems), respectively, and the immunostained cells (1 × 10^6 cells/sample) were analyzed on a FACSCalibur flow cytometer (BD Biosciences, San Jose, CA) using CellQuest software. The data were calculated as the percentage of positive cells in the cell populations.

**Intracellular staining and flow cytometry**

CD4+ T cells were cultured with SEB-loaded monocytes for 48 h in the absence or presence of either AF or PP14•Fcγy, with the addition of 3 μM monensin for the last 5 h of stimulation. The cells were harvested, washed twice in PBS, fixed in 4% paraformaldehyde for 30 min, washed twice in PBS 1% FCS, resuspended in 0.1% saponin, 1% FCS/PBS, and then stained using the appropriate anti-cytokine (IL-2, IFN-γ) (BD Pharmingen, San Diego, CA) or anti-GATA-3 Abs (Santa Cruz Biotechnology, Santa Cruz, CA) for 30 min. Cells were washed twice in PBS and analyzed.

**RT-PCR analysis of GATA-3**

Semi-quantitative analysis of GATA-3 mRNA expression was performed by culturing CD4+ T cells and SEB-loaded monocytes for 24 h, as previously described, before harvesting the cells for RNA extraction. STAT60 RNA isolation reagent (Tel-Test, Friendswood, TX) was used, according to the manufacturer’s instructions. First-strand cDNA was synthesized using random hexamer primers and Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI). PCR was performed using the following primer sequences: 5’ GADPH primer, ACCACGTCTCCAGGCT CAC; 3’ GADPH primer, TCCACACCCTGTGCTGTA; 5’ GATA-3 primer, CTCTTACCCGAGCTCCGAG; 3’ GATA-3 primer, CTCTGAT TTGGAGCATTCT, resulting in the amplification of PCR product of 372 bp (GATA-3) and 451 bp (GADPH).

**Results**

Differentiation of CD4+ T cells along Th1 and Th2 pathways is dependent, in part, on the strength of TCR signaling during early stages of T cell activation (1). Given our previous demonstration that PP14 desensitizes signaling through the TCR (5, 6), we hypothesized that PP14 may influence polarization of Th1 vs Th2 cytokine responses. To test this prediction, purified CD4+ T cells were stimulated by monocytes preloaded with SEB under nonpolarizing conditions (i.e., in the absence of polarizing cytokines, such as IL-12 and IL-4, and blocking Ab targeted at cytokines that normally drive the alternative response), and the levels of Th1 (IL-2, IFN-γ) and Th2 (IL-5) cytokines in the medium were determined. Of note, the levels of two other Th2 cytokines, IL-4 and IL-13, were also evaluated at a series of time points (between 5 h and 10 days), but their levels proved to be below the sensitivity of the ELISA (31.25 and 62.5 pg/ml, respectively; data not shown).

Stimulation with SEB, an agent that classically polarizes T cell responses toward the Th1 phenotype (23–25), actually promotes the secretion of a mixture of Th1/Th2 cytokines early on. This is reflected in the observed dose-dependent increases in secreted IFN-γ (Fig. 1A, upper panel), IL-2 (data not shown), and IL-5 (Fig. 1A, lower panel). However, the patterns for the Th1 vs Th2 cytokine responses differed. In the case of the Th1 cytokine IFN-γ, there was only minimal secretion at the lowest dose of SEB (1 ng/ml), and the dose response to higher concentrations of SEB was steep. In contrast, the Th2 cytokine IL-5 approached its plateau at 1 ng/ml SEB, and further increases in the SEB dose enhanced cytokine secretion only marginally. This pattern of dose-dependent cytokine responses is consistent with earlier reports by us (26) and others (1, 27–29) for both SEB and other Ags. Of note, while the absolute levels of cytokine secretion varied up to 10-fold between different donors, the same pattern was evident in each case.

Next, we examined the effects of AF, used in early experiments as a rich source of native PP14, on the cytokine response to SEB stimulation. Whereas AF strongly attenuated the IFN-γ (Fig. 1A) and IL-2 (data not shown) responses at all SEB concentrations, it inhibited IL-5 secretion only at low SEB concentrations, and even in this study, to a lesser extent than it inhibited IFN-γ and IL-2. In fact, at the highest SEB concentration, secretion of the Th2 cytokine IL-5 was even enhanced by AF in some experiments (Fig. 1, A and B). Fig. 1B presents data from six independent experiments, demonstrating the consistency of the differential AF effects on IFN-γ vs IL-5 responses, with greater sensitivity of IFN-γ to AF-mediated inhibition, notwithstanding interexperiment variability (with different cell and AF donors). Of note, the AF used in this study did not contain detectable levels of the cytokines under study (data not shown).

Importantly, we have previously demonstrated that PP14 accounts for the T cell inhibitory activity AF (22). In line with this report, AF that had been immunodepleted of its PP14 did not inhibit IFN-γ or IL-5 secretion (Fig. 1C), suggesting that PP14 is indeed the active factor within AF. This is consistent with our previous finding that AF depletion of its PP14 no longer inhibits IL-2 or Th cell proliferation (6). Furthermore, a rPP14 derivative, PP14•Fcγy, showed similar inhibitory effects (Fig. 1D). PP14•Fcγy significantly inhibited the secretion of IFN-γ at all SEB doses tested, while having only a marginal effect on IL-5 secretion. For these experiments, the data have been normalized against a control Fcγy fusion protein, CD99•Fcγy, which itself inhibited IL-5 secretion to some extent, especially at higher SEB doses, although it had only a marginal effect on IFN-γ secretion. The basis for this IL-5 inhibitory effect is unclear.

As a next step, we examined AF and PP14•Fcγy effects on levels of intracellular cytokines (IFN-γ and IL-4) to validate the cytokine secretion findings at the single cell level. SEB-loaded monocytes were used to stimulate CD4+ T cells, in this case for...
only 24 h, as the optimal time point for detecting IL-4-expressing cells. Cells were treated with monensin for the last 5 h of incubation, and then fixed, permeabilized, and double immunostained with cytokine-specific Abs. Given that only 10% of T cells express the TCR Vβ subtype that mediates SEB responsiveness, a relatively low percentage of immunodetectable, cytokine-expressing cells is expected. As shown in Fig. 1E, SEB induced a dramatic increase in the percentage of cells with intracellular IFN-γ. The increase in the percentage of IL-4-expressing cells was less marked, and in fact, in some experiments, IL-4 cells actually decreased at the highest SEB concentration (data not shown). Importantly, both AF and PP14•Fcγ1 significantly decreased the percentage of IFN-γ+ cells, without substantially changing the low levels of IL-4+ cell in the population (Fig. 1E). Thus, intracellular cytokine findings paralleled those with secreted cytokines, and extended the findings to a second Th2 cytokine, IL-4.

The differentiation of Th cells is influenced by regulatory cytokines, such as IL-4 and IL-12, which are present within the cells’ microenvironment during the activation process. Because IL-4 is known to polarize Th cells toward the Th2 phenotype, we compared the effects of exogenous IL-4 vs PP14 on cytokine expression under these short-term, nonpolarizing experimental conditions. To this end, CD4+ T cells were stimulated as before with SEB-loaded monocytes, and cytokine secretion (Fig. 2A) and percentage of cells expressing intracellular cytokine (Fig. 2B) were assessed. As was the case with AF and PP14, addition of exogenous IL-4 decreased IFN-γ secretion, while moderately increasing IL-5 secretion (Fig. 2A). Significantly, there was a pronounced additive effect on IFN-γ secretion when AF...
or PP14•Fcγ1 was used in combination with exogenous IL-4 (Fig. 2A, left panel). In contrast, AF actually augmented the moderate increase in IL-5 levels induced by IL-4 in the presence of high SEB concentrations; thus, AF and IL-4 in combination promoted even greater IL-5 secretion (Fig. 2A, right panel). Of note, at lower SEB concentrations, in which PP14 inhibited IL-5 secretion, the addition of exogenous IL-4 overrode this PP14-mediated inhibition (data not shown).

Intracellular cytokine analysis yielded similar parallels between exogenous IL-4 and PP14. Addition of exogenous IL-4 or PP14•Fcγ1 (or AF) each reduced the percentage of IFN-γ/H9253/H11001 cells, and notably, when used in combination, these two agents resulted in an even greater decrease in the percentage of IFN-γ/H9253/H11001 cells (Fig. 2B). In contrast, the percentage of IL-4/H11001 cells was not substantially impacted by the addition of PP14•Fcγ1 (or AF), with or without exogenous IL-4. Taken together, these findings demonstrate a parallel between PP14 and exogenous IL-4 on Th1 vs Th2 cytokine production and secretion under nonpolarizing conditions, along with a significant combinatorial effect when used together.

Chemokines, like cytokines, mold Th cell responses. As T cells differentiate along the Th1 and Th2 pathways, they acquire distinctive migratory capabilities, which are coupled to their chemokine receptor expression (30). We first surveyed the expression of a small panel of chemokine receptors (CXCR3, CCR5, CCR3, CCR7, and CXCR4) on CD4/H11001 T cells following SEB stimulation. Only CXCR3 and CXCR4 demonstrated significant up-regulation in this experimental context. However, the expression of CXCR3 upon stimulation was limited to only subpopulation of the CD4⁺ T cells, corresponding to blast-transformed cells. In contrast, all CD4⁺ T cells express low levels of CXCR4, which increases upon SEB stimulation. Next, the effects of AF and PP14•Fcγ1 on the surface expression of these two chemokine receptors were determined, using SEB-stimulated and nonstimulated CD4⁺ T cells in side-by-side analyses. As shown in Fig. 3, both AF and PP14•Fcγ1 differentially affected the two chemokine receptors, reducing the number of cells expressing CXCR3, but not CXCR4. This chemokine receptor finding is consistent with the previous cytokine findings, in that PP14 preferentially inhibits the chemokine receptor expressed at high levels on Th1 cells and very low levels on Th2 cells (CXCR3), but not CXCR4. This chemokine receptor finding is consistent with the previous cytokine findings, in that PP14 preferentially inhibits the chemokine receptor expressed at high levels on Th1 cells and very low levels on Th2 cells (CXCR3), but not CXCR4. This chemokine receptor finding is consistent with the previous cytokine findings, in that PP14 preferentially inhibits the chemokine receptor expressed at high levels on Th1 cells and very low levels on Th2 cells (CXCR3), but not CXCR4. 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representative of three separate experiments. or CXCR4, and 10^4 cells were analyzed by flow cytometry. FITC-conju-
harvested and stained with FITC-conjugated Ab specific for either CXCR3
immunostaining and flow cytometric analysis in T cells activated for 72 h
experiments is shown.

FIGURE 3. PP14 selectively inhibits the expression of CXCR3, but not
CXCR4. T cells were stimulated with monocytes loaded with SEB, in the
absence or presence of either AF or PP14•Fc-y1. After 48 h, cells were
harvested and stained with FITC-conjugated Ab specific for either CXCR3
or CXCR4, and 10^4 cells were analyzed by flow cytometry. FITC-conju-
gated mouse IgG1 and IgG2a Ab were used as isotype controls, respect-
tively. The percentage of CXCR3-positive cells is shown in the upper
panel, and the level of CXCR4 expression is shown in the lower panel.
Dashed line, isotype control; dotted line, unstimulated cells; gray line, SEB
stimulation; black line, SEB stimulation in the presence of AF; gray thick
line, SEB stimulation in the presence of PP14•Fc-y1. The results shown are
representative of three separate experiments.

of PP14•Fc-y1 or AF (Fig. 4A). Furthermore, these GATA-3
mRNA findings were corroborated at the protein level by immu-
nofluorescence and flow cytometric analysis of intracellular
GATA-3 (Fig. 4B). Thus, while GATA-3 protein was reduced after
SEB stimulation, PP14•Fc-y1 prevented this down-regulation,
maintaining it at the level found in unstimulated cells. This PP14-
mediated interference with the repression of a transcription factor
required for Th1 differentiation is consistent with a role for PP14
in promoting a Th2 phenotype.

Taken together, these results support a model wherein PP14
differentially inhibits Th1 vs Th2 responses during T cell priming,
therefore driving the polarization of Th2 cells.

Discussion
PP14 (glycodelin) is a pregnancy-associated protein with unique
immunoregulatory properties. Our early data established that PP14
acts directly on T cells, targeting early events during TCR signal-
ing (22). PP14 decreases the stability of TCR-induced phospho-
proteins (5), which is linked to desensitization of TCR signaling
and elevation of T cell activation thresholds (6). In this way, PP14
has opposite effects to costimulation through CD28 (37). Other
mechanistic clues lie in the dependence of the T cell inhibitory
activity of PP14 on the surface phosphatase CD45 (7), suggest-
ing that PP14 may somehow interfere with the transit of CD45
and perhaps other components in and out of APC:T cell contact
sites (5).

Knowing that PP14 desensitizes TCR signaling (6), and that the
strength of TCR signaling dictates how T cell responses evolve (1,
26–29), we now hypothesized that PP14 may differentially affect
Th1 vs Th2 commitment during primary T cell activation.

The specific findings bearing upon the impact of PP14 on Th1 vs
Th2 responses include the following: 1) Th1 (IFN-γ) and Th2
(IL-5 and IL-4) cytokine responses, as determined by cytokine
secretion and intracellular cytokines, exhibit differential sensitivity
to PP14-mediated inhibition; 2) PP14 parallels exogenous IL-4, a
well-established Th2-polarizing cytokine, in its ability to skew cy-
kine responses toward a Th2 phenotype under nonpolarizing
conditions; 3) PP14 selectively inhibits the expression of a che-
mokine receptor (CXCR3) associated with cells of the Th1 sub-
type, but not one of the Th2 subtype (CXCR4); 4) PP14 prevents
the repression of the transcriptional factor GATA-3, an event that
is essential for differentiation along the Th1 lineage.

The early balance between Th1 and Th2 cytokine output during
primary T cell activation is dictated in part by the strength of TCR
signaling, which in turn is influenced by factors such as antigenic
dose and the nature of the Ag (1, 26–29). Thus, while both Th1
and Th2 cytokines are expressed simultaneously, low doses of
stimuli primarily induced Th2 cytokines (IL-4 and IL-5), with low
to undetectable levels of Th1 cytokines (IL-2 and IFN-γ), whereas
priming with higher doses of stimuli favored increased production
of Th1 cytokines. The Th1 skewing was correlated with the in-
duction of ERK phosphorylation (26), and blocking this phosphor-
ylation event specifically blocks the Th1 response (38). The ob-
served effects of PP14 on early cytokine output can be readily
understood within this framework. As one would have predicted
for an agent that can attenuate the strength of TCR signaling,
PP14, at each antigenic dose, tips the balance in favor of Th2
cytokines that require less TCR triggering. Accordingly, the low
level IFN-γ production elicited by intermediate doses of SEB is
completely ablated by PP14, in contrast to the IL-4 and IL-5 pro-
duction at these doses of SEB, which are only partially blocked by
PP14. At high doses of SEB, IFN-γ secretion is significantly in-
hibited by PP14, while IL-4 and IL-5 production is only slightly
affected or even augmented.

This study focused on early events after T cell encounter with
Ags, and thus, the experiments were performed under nonpolariz-
ing conditions and with a relatively short duration of Ag exposure.
Nonetheless, our findings in this context are most likely relevant to polarization. Due to the cross-regulatory and self-propagating properties of cytokines, IL-4 and IFN-γ in particular (1), the early secretion of such cytokines, and their balance, soon after T cell stimulation, is a major determinant in directing polarized responses. Thus, even minor changes in the early cytokine microenvironment elicited by agents such as PP14 are likely to stochastically influence population dynamics and polarize responses over time skewed to the Th2 subset.

The cytokine secretion and intracellular cytokine data pointing to the contribution of PP14 to Th2 skewing were reinforced by analysis of the GATA-3 transcriptional factor, which plays a pivotal role in Th2 differentiation. Our key finding was that PP14 blocks TCR-induced down-regulation of GATA-3 expression in CD4+ T cells, which conveniently explains PP14’s preferential inhibition of Th1 responses and skewing toward Th2 cytokine output. Normally, GATA-3 expression is high in naive T cells and down-regulated upon TCR triggering. Importantly, GATA-3 is strongly expressed in Th2, but not Th1 cells. This expression profile is functionally significant, because GATA-3 directly inhibits Th1 cytokines by a cell-intrinsic mechanism and independently augments Th2-specific cytokines (39). A feedback pathway is established that stabilizes Th2 commitment and antagonizes Th1 commitment (40). GATA-3 has thus emerged as a master switch in established that stabilizes Th2 commitment and antagonizes Th1 responses. Indeed, our findings with desensitized PP14-treated T cells parallel those with hyporesponsive cells derived from Rlk−/− knockout mice, lacking two Tec family kinases that are essential for phospholipase Cγ activation (35). TCR signaling is desensitized in T cells from Rlk−/− mice, and significantly from our standpoint, this is accompanied by impaired repression of GATA-3 expression and concomitant skewing to Th2 responsiveness. Another interesting parallel is that for both Rlk−/− and PP14-treated cells (22), TCR desensitization can be overcome by stimulating with PMA and ionomycin, pharmacological activators that together circumvent early TCR signaling events.

The main aspect of our findings is that we have linked PP14 to Th2 skewing, as documented by patterns of cytokine and chemokine expression, and lineage-specific transcriptional factor modulation. There are a growing number of features of PP14-mediated inhibition that we have documented to date. These include decreased duration of TCR-induced phosphorylated substrates (5), CD45 phosphatase dependence (7), and localization of PP14 to APC:T cell contact sites (5). Perhaps the most intriguing aspect of the T cell immunoregulatory function of PP14 is its rheostatic mechanism for T cell inhibition based on elevation of TCR activation thresholds (6), in contrast to costimulation through CD28, which functionally lowers T cell activation thresholds (37). Incorporating these various molecular and subcellular events into a unified model will not be simple because they are complex and dynamic. This complexity and dynamism are reflected in our temporal summation model (41), which pictures T cell activation as a progressively self-reinforcing process, rather than a one-pass linear sequence. However, the association of strength of TCR signaling with Th1 and Th2 lineage determination has been widely documented (1, 27–29), and PP14, by acting as a regulator of TCR signaling strength, may represent an important determinant in lineage decision of naive T cells.

Previously, we raised the possibility that PP14 may account, at least in part, for some of the interesting immunological features of pregnancy (5). One of these is the amelioration of certain cell-mediated autoimmune diseases that occurs during pregnancy. Interestingly, pregnancy is reportedly associated with a Th2 shift in humans, and this could be important in the protective effect of pregnancy, because cell-mediated autoimmunity is driven by Th1 responses. PP14, which is present at high levels in maternal serum, could thus be a critical driver in pregnancy’s Th2 shift and the associated improvement in autoimmunity. Another recent immunological observation is that the predominant NK lymphoid subset within the decidua of pregnancy expresses PP14 (16). This provocative finding, along with the high abundance of PP14 in AF, raises the possibility of additional contributions of PP14 to pregnancy and fetal protection.

References


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