Hindawi Publishing Corporation
PPAR Research
Volume 2013, Article ID 970276, 8 pages
http://dx.doi.org/10.1155/2013/970276

Review Article

The Role of PPARs in Placental Immunology: A Systematic Review of the Literature

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Received 30 November 2012; Accepted 18 February 2013

Academic Editor: Regina Ensenauer

Pregnancy is a state of immunotolerance, and pregnancy outcome is strongly linked to the correct activation and balancing of the maternal immune system. Besides abortion as possible result of improper early pregnancy development, other pregnancy associated conditions like preeclampsia (PE), intrauterine growth retardation (IUGR), preterm labour, or gestational diabetes mellitus (GDM) are linked to immunologic overactivation and dysregulation. Both the innate and the adaptive immune system, and therefore B and T lymphocytes, natural killer cells (NK), macrophages and dendritic cells (DCs) are all involved in trophoblast invasion, pregnancy maintenance, and development of pregnancy disorders. Peroxisome proliferator activated receptors (PPARs) are nuclear transcription factors with three known isotypes: PPARα, PPARβ/δ, and PPARγ. They are expressed in most human organs and their function extends from regulating metabolism, homeostasis, and carcinogenesis to immune response. In the recent years, PPARs have been identified in most reproductive tissues and in all lines of immune cells. Only in few cases, the role of PPARs in reproductive immunology has been elucidated though the role of PPARs in immune answer and immunotolerance is evident. Within this paper we would like to give an update on today's knowledge about PPARs and immune cells in reproduction and highlight interesting interferences in regard of future therapeutic targets.

1. Introduction

Trophoblast invasion at the beginning of pregnancy development is often described in the context of pregnancy complications. The underlying pathophysiology includes elevated macrophage populations hampering trophoblast invasion and inducing trophoblast apoptosis [1, 2]. As another, even bigger part of the innate immune response decidual natural killer (dNK) cells have been identified in promoting trophoblast invasion [3] and reduced numbers of dNK have been reported associated with IUGR [4]. The components of the adaptive immune system present at the fetomaternal interface as the site of immunologic tolerance plays an important role in balancing the maternal immune response to the fetal allograft. For many years a simplified approach to this complex process of immunotolerance was postulated. Thus pregnancy was regarded as a phenomenon of T helper cells subgroup 2 (Th2) going along with inhibition of T helper cells subgroup 1 (Th1) and their cytotoxic effects [5]. However the results of the last years have shown that cytokines associated with Th1 are closely linked to a positive pregnancy outcome [6]. Besides this formerly used concept of Th1 and Th2 immune response additional Th17 cells and regulatory T cells (T reg) have been described to show their importance concerning pregnancy outcome. In PE T reg have been shown to be reduced in number [7], whereas regular pregnancies go along with increased numbers of T reg [8]. The importance of the adaptive and innate immune system at the fetomaternal interface, that is, the extra villous trophoblast (EVT), is obvious not just in terms of late term pregnancy complications such as PE or IUGR but even more when talking about miscarriages and maintaining early pregnancy. In this context not only T cell regulation has been described but also macrophage population and its dynamic polarization seem to play a role concerning the success of early pregnancy [9].

As part of the nuclear hormone receptor (NHR) superfamily peroxisome proliferator activated receptors have been discovered in the year 1990. They act as ligand activated transcription factors binding to DNA as heterodimers with retinoid X receptor (RXR) inducing transcription of various

genes [10]. Their function is triggered by the shape of the ligand binding domain and by coactivator and corepressor proteins. Among those are free fatty acids and eicosanoids that are, mostly prostaglandins and leukotrienes [11]. Originally PPARs were mostly associated with metabolic aspects as fatty acid transport or oxidation [12]. However, PPARs have been identified to play an important role in carcinogenesis, homeostasis, and immune system. Both the innate and the adaptive immune system, are strongly influenced by PPAR activation triggering macrophages and other leukocyte populations such as lymphocytes and dendritic cells [13, 14]. Concerning placenta as the spot of feto-maternal immunotolerance PPARs and their effect on macrophage population and polarization as well as lymphocyte differentiation have come to scientific interest and basic research on this aspect of placental immunology has been done over the past years. Within this paper we would like to show interesting findings on the field of PPAR research in placental tissue and point out recent findings of PPAR influence on macrophages and T lymphocytes in general thus encouraging further research in the field of PPAR and placental immune response.

2. Material and Methods

By searching PubMed 942 relevant studies up to November 2012 were identified. Only publications in English language were selected. Following keywords were used individually and in combination. PPAR, macrophages, T lymphocytes, B lymphocytes, placenta, and reproduction. A systematic literature review was conducted using the literature provided and based on our findings and experience in PPAR function in female reproduction. Relevant information on PPAR and macrophages and lymphocytes in reproductive context were gathered to offer an updated summary on this topic.

3. PPARs and Reproduction

By now three isotypes of PPAR, that is, PPARα, PPPARβ/δ, and PPARγ have been described [15]. All three are expressed in human placenta and different functions have been attributed to them. Interestingly concentration and function of PPAR isotypes in placenta change throughout pregnancy in humans and in animal models [16, 17]. For PPARγ and PPARβ/δ a role in trophoblast differentiation, trophoblast invasion, and decidualization has been established [17, 18]. Also for PPARα there is evidence for its supportive role in placental development and creating an anti-inflammatory placental environment by negatively effecting lipid peroxidation and production of nitric oxide (NO) [19]. Concerning PPARβ/δ its importance and positive effect on placentation timing and uterine angiogenesis has been shown in the mouse model [20]. PPARγ is by now well established in several aspects of placenta biology such as regulation of trophoblast invasion and early development. It has been shown to modulate the expression of proinflammatory genes such as matrix metalloproteinases [21]. A supposedly detrimental role for PPARγ has been described in the case of human cytomegalovirus (HCMV) as the virus is causing an activation of PPARγ and therefore hampering invasion of the trophoblast [22]. Concluding the preliminary research PPARγ seemingly takes the most important role among the three isotypes in placenta differentiation and immunology.

3.1. PPARα. PPARα is highly expressed in various organs such as liver and heart, where PPARα regulates lipid metabolism and anti-inflammatory pathways [23, 24]. So far PPARα has also been identified in placenta and different fetal organs in postplacentation period [25]. In a rat model changes of PPARα concentration were shown to appear during the course of pregnancy and its activation was linked to a negative regulation of lipid peroxidation and nitric oxide (NO) production [26]. In mice adverse reproductive outcomes in the context of disrupted carbon-1 metabolism could be attributed to PPARα effects, which lead to an imbalance in the Th1 : Th2 ratio through increased maternal and fetal interferon γ (IFNγ) and decreased maternal interleukine 10 (IL-10) [27]. Perturbations in PPARα caused by a disruption of carbon-1 metabolism showed also anti-inflammatory effects of PPARα by increasing the production of Th2 cytokines IL-10 and IL-4 and by reducing the production of Th1 specific cytokines like IFNγ and IL-2 in a mouse model [28].

Contrarily to former statements PPAR alpha seems to have impact on pregnancy outcome by influencing T cell differentiation and therefore T cell specific cytokine production.

3.2. PPARβ/δ. PPARβ/δ, which is also referred to as PPARβ or PPARδ, is encoded by one gene (nuclear receptor subfamily 1, group C, member 2; NR1C2) and belongs to the well-discussed family of PPARs and is highly expressed at the human placenta [29]. Its role in pregnancy development and maintaining pregnancy has been shown for both uterine and embryonic PPARβ/δ by stating their pivotal roles in placental angiogenesis and on time placentation [30]. PPARβ/δ null mice showed reduced birth weight and placental defects hereby underlining the importance of PPARβ/δ for placental function [31]. An in vitro model of trophoblast cells has shown further implications of PPARβ/δ effects on enzyme expression in trophoblast cells. 11-hydroxysteroid dehydrogenase type 2 (11-HSD2), which is responsible of protecting the fetus from exposure to high levels of maternal glucocorticoid, seems to be repressed by activation of PPARβ/δ, consecutively causing IUGR. Leaving out in vivo coactivation effects on 11-HSD2, which might influence its expression and function, it is attempting to speculate whether over-expression of PPARβ/δ is linked to placental pathologies via this pathway [32]. Impact of PPARβ/δ on inflammation processes has been shown in central nervous system autoimmunity by reducing inflammatory T cells. In both mouse and human immune cells PPARβ/δ was found to reduce production of IFNγ and IL-12 family cytokines and expansion of CD 4+ cells hereby reducing the inflammatory reaction [33]. Concerning miscarriages PPARβ/δ expression has been shown to be enhanced in miscarried placentas whereas leptin expression appeared to be low [34]. Obviously PPARβ/δ cannot attribute a clear pro- nor an anti-inflammatory function at this point of time; however its presence and importance in immune response is indisputable.

3.3. PPARγ. PPARγ alike the other PPAR isotypes was at first described in its role in metabolic control and homeostasis gaining importance because of its highly efficient ligands, which are currently made use of in diabetes therapy. Further studies have shown its role in trophoblast function and invasion and treatment with PPARγ agonists led to fetal and placental growth restriction in a PPARγ dependent manner [35, 36]. Contrarily rats treated with PPARγ antagonists demonstrated impaired placentation and placental differentiation, thus implying differences in effect of PPARγ activation or blocking according to the stage of pregnancy development [37]. In regard of IUGR and obesity PPARγ expression was found to be increased in human placenta; hereby this upregulation could be interpreted as adaptive response to the IUGR placenta preventing insufficient nutrient supply [38, 39]. Alternatively PPARγ expression could be seen as causative for IUGR and placental failure as it was shown in different studies based on PPARγ specific activation [36, 40]. Mouse knockout models reacted with fetal loss in early pregnancy due to the missing PPARγ expression and showed placental defects [31]. Further studies with continuous PPARγ antagonist treatment in uncomplicated rat pregnancies have provided evidence for the pivotal role of PPARγ in development of PE, as this treatment led to an increase in soluble fms-like tyrosine kinase 1, which is strongly linked to the pathogenesis of PE. Therefore PPARγ might offer a potential therapeutic target for the treatment and prevention of PE [41].

Additionally research on human placentas has been able to show the importance of PPARγ in cytokine production as IL-6, IL-8, and TNFα were reduced by PPARγ ligands troglitazone and 15d-PGJ2 [42].

In Macrophages stimulated with IL-4 PPARγ is markedly induced [43] and therefore further investigation was done to elucidate the role of PPARγ in alternative activation of macrophages. In a mouse model setting of high caloric uptake alternative activation of macrophages was not possible without PPARγ expression and therefore affected individuals were more prone to obesity and insulin resistance [44].

4. PPAR Activation in Macrophages

Among the immune cells regulating early pregnancy development and implantation T cells and NK cells have been essentially described. At the site of trophoblast invasion decidual macrophages are the second most predominant cell line. Producing inflammatory cytokines and presenting antigen they are known to regulate T-cell activation and therefore apoptosis [45].

According to today's research findings about macrophages two classical phenotypes are known—M1 as inflammation phenotype and M2 as promotor of immune modulation. Considering pregnancy as state of balancing immune tolerance at the fetomaternal interface M2 phenotype would be expected in regular pregnancy development and M1 would be linked to miscarriage or failure of implantation. As macrophage plasticity has been demonstrated to be dynamic in character this more or less simple model of thought has lost its importance [46]. It seems obvious that macrophages, which are increased in number in cases of spontaneous miscarriage [15], can react to external stimuli and conditions and therefore a more complex function of macrophages in terms of reproductive immunology is considered. Macrophages stimulated by IFNγ differentiate into the classically activated (M1) phenotype, thus implying inflammation and activation of T-lymphocytes. On the other hand IL-4 can induce macrophage differentiation into the alternatively activated (M2) phenotype via expression of PPARγ and PPAR gamma activator [47]. By its transrepressive action PPARγ can also stop the nuclear factor kappa B (NFκB) mediated production of pro-inflammatory mediators [48]. Leishmania infection, for example, benefits from infiltrating macrophages and from Leishmania parasites producing PPARγ ligands that lead to inactivation of the destructive inflammation response. Thus PPARγ activation leads to M2 differentiation and consequently allows an immunomodulatory response and chronic stage in this parasitary disease [49]. Further evidence for PPARγ effects on macrophage activation and differentiation comes from a transgenic mouse model. Macrophage specific PPARγ deletion led to diet associated obesity, insulin resistance, and glucose intolerance [44]. The effect of PPARγ activation on macrophage differentiation became even clearer in the field of atherosclerosis, where monocytes developed into enhanced M2 phenotype after PPARγ activation. Additionally these M2 macrophages implemented more pronounced anti-inflammatory components of M1 macrophages. This interference with activated M1 macrophages is transported via negative influence on proinflammatory signaling pathways such as activating protein 1 (AP-1), signal transducer activator of transcription (STAT-3) and NFκB [50, 51]. Interestingly this effect of PPARγ is operating mainly in presence of adequate stimulation for monocytes into M2 macrophages such as IL-4 and not in already differentiated M1 phenotypes. This observation in the field of atherosclerosis could be demonstrating limitations to macrophage plasticity. Macrophage plasticity, which is obviously strongly PPAR dependent, has also been shown in pregnancy development and maintenance [52]. Macrophages are highly active in phagocytosis of apoptotic cells in order to reduce autoimmune response to self-antigens during pregnancy. PPARδ has been shown to be highly expressed in such macrophages and can attribute a pivotal role in clearance of apoptotic cells by macrophages. In case of PPARδ deletion in macrophages a decrease in opsonin expression like C1qb and therefore impairment of phagocytosis is the result [53].

5. PPARs in Other Immune Cells

Various leukocyte populations express PPARγ and therefore a role in immune response of lymphocytes and dendritic cells is suggested for this transcription factor [14]. PPARα has been described as suppressor of Th1 immunity and promotor of Th2 immunity [27, 28, 54]. As Th1 and Th2 cytokines have contrary effects on human pregnancy T cell differentiation towards Th1 has been identified as one of the major reasons for abortion, IUGR and PE [55, 56]. Decreased levels of maternal PPARα have been brought into causative context with an imbalance in Th1 : Th2 ratio leading to increased IFNγ and reduced maternal IL-10 and therefore implicating

miscarriage and abortion [27]. PPARβ/δ has been proved to be an important negative regulator in central nervous system autoimmune inflammation. Besides of the inhibition of IFN-γ and IL-12 family cytokines PPARβ/δ has been attributed an important role in downregulation CD 4+ T cell population [57].

15-Deoxy-Δ-Prostaglandin J2 (15d-PGJ2), which is an endogenous prostaglandin and acts as ligand for chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), has been shown to suppress the expression of NFκB, which leads to a decrease in Th1 cell cytokines IFNγ and TNFα. Activation via PPARγ and therefore therapeutic approach via PPAR agonists has been ruled out explicitly for this regulatory mechanism in amnion and myometrial cells [58]. Whether 15dPGJ2, which is also a ligand for PPARγ, is furthermore capable of promoting an anti-inflammatory shift in cytokine production via PPARγ is still to be elucidated.

An important part of the adaptive immune system is taken over by B lymphocytes, which differentiate into immunoglobulin-producing plasma cells therefore setting up the basis for humoral immune response [59]. B lymphocytes that have been described quantitatively changed in cases of recurrent abortion, for example, caused by antiphospholipid syndrome [60]. Concerning the role of B lymphocytes on PE pathophysiology extensive research has identified them as pro-inflammatory agents by mass producing of immunoglobulin and therefore promoting hypertensive reaction via angiotensin II type I receptor (AT1-AA) [61]. Depletion of B cells in this context led to lower blood pressure response to placental ischemia and lower levels of TNFα [62]. Expression of PPARγ has been described for normal and malignant B cells and additionally certain types of PPAR ligands were identified to inhibit B cell proliferation [63]. Activated B cells upregulate their expression of PPARγ and beyond this PPAR ligands such as 15d-PGJ2 (endogenous) and rosiglitazone (synthetic) proofed to stimulate B cell proliferation and differentiation. Furthermore PPARγ ligands enhanced the expression of cyclooxygenase 2 (Cox-2) and the plasma cell transcription factor BLIMP-1. Antagonists, however, showed the reverse effect on B cell population [64].

NK cells are the most abundant immune cell population at the site of implantation and have been long recognized as important regulators in early pregnancy maintenance partially in cooperation with dendritic cells (DCs) [65]. Underlining this statement DCs have been reported to elevate induction of regulatory T reg due to crosstalk with uterine NK cells and uterine DC to enhance proliferation of NK cells producing IL-10 [66, 67]. Obviously both cell types contribute to regular implantation as depletion mice models for each cell type have shown [68]. Production of IFNγ and cytolytic activity are two major functions of NK cells; both functions being essential for innate immunity [69]. PPARγ ligands were reported to influence both functions via PPARγ and without this pathway. The natural PPARγ ligand 15d-PGJ2 and the synthetic ligand ciglitazone both reduce the production of IFNγ via PPARγ expression. However cytotoxic activity of NK cell seems not affected by PPARγ expression. Interestingly IFNγ levels were decreased by 15d-PGJ2 even without influencing PPARγ expression, suggesting that this effect takes place at a posttranscriptional level [70].

DCs are extensively described as antigen presenting cells triggering the T cell immune response and T cell differentiation also in reproductive organs. Their importance in decidualization and vascularization has been shown in depletion models of mice [68]. PPARγ has been found to prevent IL-12 production, which is indispensable for Th1 differentiation and therefore PPARγ might shift naïve T cells to Th2 via its effect on DC [71, 72].

6. Summary

Placental architecture and function play a crucial role in fetal development and pregnancy maintenance. Correct placental differentiation and trophoblast invasion are highly important preconditions for fetal growth and appear to be altered in several pregnancy complications. PE, IUGR, and GDM are strongly linked to placenta changes [73, 74]. Each of these pregnancy related disorders shares similar risk factors and comes along with an elevated risk for developing the other [75, 76]. Risk factors include obesity, hypertension, previous episodes of GDM, PE or IUGR and a family history of such disorders [77, 78]. Common risk factors allow to draw conclusions on common aspects of pathophysiology highlighting improper placentation, processes of inflammation and elevated levels of cytokines and oxidative stress [79–81].

Mostly PPARβ/δ and PPARγ have been identified in macrophages influencing differentiation and cytokine production to an anti-inflammatory profile. Considering the well described dynamic plasticity of macrophages especially in terms of pregnancy related tolerance PPAR ligands could evolve to an interesting therapeutic agent by promoting the M2 phenotype and therefore improving pregnancy development and reducing glucose intolerance. In analogy to the formerly proposed model of M1 versus M2 distribution of macrophage population the paradigm of pregnancy as Th2 phenomenon has been left. However, the Th1 : Th2 ratio still plays an important role in pregnancy as T cell specific cytokine production is essential for immunotolerance at the fetomaternal interface. PPARβ/δ and PPARγ have been described as promotor of the anti-inflammatory Th2 differentiation [54, 57]. Besides endogenous PPARγ ligands (15d-PGJ2) other synthetic ligands have been shown to promote an anti-inflammatory cytokine profile in Th1 and Th2 cells; however it remains unclear if all these effects are induced via PPAR activation [58]. The potential effect of PPAR ligands on T cell differentiation would still be a promising approach to the treatment of inflammatory activation in pregnancy. B lymphocytes considering pregnancy disorders mostly associated with PE have been shown to get activated by PPAR agonists and a reverse effect was described for PPAR antagonists [64]. In a similar way NK cells can be influenced by endogenous and synthetic PPAR ligands. However this influence seems to be limited to their cytokine production [70].

Looking at therapeutic strategies in order to prevent loss of pregnancy or miscarriage changing Th1 immune response [82] via PPAR activation could be a reasonable solution. Use

of PPARγ agonists could be useful in preventing preterm labour by reducing inflammatory response within the fetal membranes [83]. Also lifestyle and nutrition changes could become recommendable according to PPARγ actions as linoleic acid as component of vegetables, fruits, grains, seeds, and others is easily converted to a ligand of PPARγ by the gut flora in combination with probiotics [84].

Summing up PPARs evidently play an important role in immune cell differentiation and interaction of the innate and adaptive immune system. They offer various opportunities for therapeutic approach assuming that further research is done in order to elucidate their range of effects on immune response reaching from pro- to anti-inflammatory. So far immune cells in reproduction have been focused intensively concerning early and late pregnancy; however, knowledge about PPAR activation effects on immune cells concerning especially pregnancy issues is limited. As PPAR activation of immune cells and the importance of immune cells in pregnancy are both well described further research in this field is very promising in terms of understanding placental immunology and finding therapeutic targets.

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