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REVIEW

PPAR-γ – a possible drug target for complicated pregnancies

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Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors expressed in trophoblasts, which regulate both cell differentiation and proliferation. In recent years, evidence has linked PPARs to playing an integral role in pregnancy; specifically, PPAR-β and PPAR-γ have been shown to play an integral role in placentation, with PPAR-γ additionally serving to regulate trophoblast differentiation. Recent evidence has shown that PPAR-γ expression is altered in many complications of pregnancy such as intrauterine growth restriction (IUGR), preterm birth, pre-clampsia and gestational diabetes. Thus, at present, accumulating evidence from the literature suggests both a pivotal role for PPAR-γ in the progression of a healthy pregnancy and the possibility that PPAR-γ may act as a therapeutic target in complicated pregnancies. This review aims to provide a succinct and comprehensive assessment of the role of PPAR-γ in normal pregnancy and pregnancy complications, and finally its potential as a therapeutic target in the treatment and/or prevention of adverse pregnancy outcomes.

Abbreviations

ET-1, endothelin-1; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IKK, IκB kinase; RXR, retinoid X receptor; SO, superoxide; TXA2, thromboxane A2; VCAM-1, vascular adhesion molecule-1

Introduction

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors that regulate the expression of a number of genes involved in cell differentiation and proliferation (Mueller *et al.*, 1998), energy homeostasis, fatty acid catabolism and adipogenesis (Kastner *et al.*, 1994; Mangelsdorf *et al.*, 1995; Escher and Wahli, 2000; Lazennec *et al.*, 2000; Willson *et al.*, 2000). In terms of the PPAR subtype, PPAR-γ, it has been suggested that this receptor has an integral role in the progression of pregnancy; and although much of the data relating to this proposed role has been obtained from experimental animal studies, as PPARs are highly conserved across species (>80% of amino acid homology; Guan *et al.*, 1997; Kersten *et al.*, 2000), these findings may be relevant to human pregnancy and complications of human pregnancy. PPARs possess a variety of beneficial functions and as a consequence have been suggested as therapeutic targets in a number of pathophysiological conditions, including polycystic ovarian syndrome (Azziz *et al.*, 2001), type II diabetes, myocardial infarction (Cao *et al.*, 2007), multiple sclerosis, endometriosis (Feinstein *et al.*, 2002; Aytan *et al.*, 2007) and more recently Alzheimer's and Parkinson's disease (Mandrekar-Colucci and Landreth, 2011; Sadeghian *et al.*, 2012). The role of PPAR-γ in pregnancy (in particular trophoblast development) (Parast *et al.*, 2009) and complications of pregnancy such as intrauterine growth restriction (IUGR; Challis *et al.*, 2009), pre-clampsia (McCarthy *et al.*, 2011a) and gestational diabetes (Heude *et al.*, 2011) has been extensively studied over recent years. This review aims to provide a succinct summary of the role of PPAR-γ in normal pregnancy and pregnancy complications.

PPARs

The PPAR nuclear receptor family is comprised of three isotypes: α, β and γ, all of which are encoded for by distinct single copy genes located on human chromosomes 22 (α), 6 (β) and 3 (γ) (Greene *et al.*, 1995; Yoshikawa *et al.*, 1996). Throughout the body, all three isotypes differ in their tissue distribution and function. PPAR-α is predominantly

expressed in both the liver and brown fat and plays a role in lipid homeostasis via the up-regulation of the expression of enzymes involved in fatty acid oxidation/catabolism (Issemann and Green, 1990; Lee *et al.*, 1995). PPAR-β (also called δ and NUC1) is the least understood of the three human PPAR isotypes. PPAR-β has been implicated in lipid metabolism, cell survival, wound healing, embryonic implantation and development of the central nervous system (Berger *et al.*, 2005). PPAR-β also appears to have an essential role to play in placentation in addition to that of PPAR-γ. Elevated PPAR-β expression has been detected at implantation sites and in decidual cells in the rat uterus (Lim and Dey, 2000). The absence of PPAR-β in a PPAR-β knockout (PPAR-$\beta^{-/-}$) murine model resulted in severe placental defects including abnormally loose connections between the placenta and the decidua, a smaller than normal placental labyrinth, and the occurrence of severe maternal haemorrhages into the labyrinth zone (Barak *et al.*, 2002). As a consequence of these malformed placentas, PPAR-$\beta^{-/-}$ mice are associated with a high degree of embryonic death, and any surviving pups are characterized by severe fetal growth restriction.

PPAR-γ has four isoforms, γ1, γ2, γ3 and γ4, and is involved in the control of adipocyte differentiation, lipid storage (adipogenesis) and macrophage differentiation. PPAR-γ1 is expressed throughout the body, including endothelial cells (Satoh *et al.*, 1999; Diep and Schiffrin, 2001), vascular smooth muscle cells (Law *et al.*, 2000), cardiomyocytes (Park *et al.*, 1997) and macrophages, including the foam cells of atherosclerotic lesions (Fajas *et al.*, 1997; Ricote *et al.*, 1998; Spiegelman, 1998; Tontonoz *et al.*, 1998; Desvergne and Wahli, 1999). In contrast, PPAR-γ2 expression is more conservative, and this PPAR-γ subtype is found in adipocytes and the liver (Rangwala and Lazar, 2004) and regulates the action of insulin on skeletal muscle and adipose tissue (Willson *et al.*, 2001; Berger *et al.*, 2005; Sharma and Staels, 2007).

The mechanism of action of the PPARs is described in detail elsewhere (McCarthy *et al.*, 2011b). In brief, PPAR is composed of five modular domains with domain E acting as the ligand binding domain. Domain E mediates ligand-dependent transcriptional activation (Berger and Moller, 2002), which induces conformational changes in these receptors, leading to recruitment of cofactor proteins/co-activators and the subsequent heterodimerization of these receptors with the retinoid X receptor (RXR) (Kliewer *et al.*, 1992a,b). Following activation, PPARs may regulate gene expression in one of two ways, either via transactivation or transrepression. During transactivation, the co-activators interact with nuclear receptors in a ligand-dependent way and influence the set of genes transcribed. In contrast, PPAR-γ mediated transrepression suppresses gene transcription by negatively interfering with other signal-transduction pathways, such as the NF-κB signalling pathway, in a DNA binding independent manner (Chinetti *et al.*, 2000; Rosen and Spiegelman, 2001; Yki-Jarvinen, 2004). The action of PPAR-γ does not always involve direct DNA binding to regulate gene transcription. The conformational changes that occur on ligand binding allow further interaction with co-activators containing histone acetyl-transferase or co-repressor release. These co-activators include steroid receptor co-activator 1 and PPAR-γ co-activator 1, through which PPAR-γ can then indirectly exert its effects (Lehrke and Lazar, 2005).

PPAR-γ in healthy pregnancy

In mice, the role of PPAR-γ in the regulation of trophoblast activity appears to be essential as early as gestational day 10, at which time the nutritional support of the developing embryo switches from the primary yolk sac to the placenta. In the rat, low levels of expression of PPAR-γ are detected at day 11 (equivalent to mouse gestational day 9), with maximal levels detected at day 13 and subsequent down-regulation of the nuclear receptor by day 15 (Asami-Miyagishi *et al.*, 2004). The vital role of PPAR-γ in embryonic development appears to be restricted to the placenta. In humans, circulating activators of PPAR-γ (fatty acids and lipid metabolites) are elevated in normal pregnancy (approximately twofold), suggesting that PPAR-γ may act as a regulator of maternal metabolism and immune function in normal pregnancy (Waite *et al.*, 2000). Furthermore, humans with heterozygous PPAR-γ mutations exhibit partial lipodystrophy, severe insulin resistance, hypertension and steatohepatitis, all of which are classic hallmarks of pre-clampsia, a pregnancy-specific condition characterized by maternal hypertension and proteinuria (Barroso *et al.*, 1999; Agarwal and Garg, 2002; Hegele *et al.*, 2002; Savage *et al.*, 2003).

Within the human placenta, PPAR-γ is expressed predominantly in trophoblasts and is required not only for trophoblast differentiation but also for trophoblast maturation to establish maternal fetal transport (Schaiff *et al.*, 2000; Rodie *et al.*, 2005). During the first trimester, PPAR-γ protein is expressed primarily in villous cytotrophoblasts and invading extravillous trophoblasts as early as 7 weeks of human gestation (Wang *et al.*, 2004). In the second trimester, PPAR-γ expression is detected in columns of the anchoring villi and cytotrophoblasts (Waite *et al.*, 2000). In contrast, PPAR-γ is not detected in non-invasive, differentiated syncytiotrophoblasts in either of the first or second trimesters (Waite *et al.*, 2000; Capparuccia *et al.*, 2002; Rodie *et al.*, 2005). Furthermore, for PPAR-γ expression in the third trimester, human placenta is localized to villous syncytiotrophoblasts, as well as villous and extravillous cytotrophoblasts (Schaiff *et al.*, 2000; Tarrade *et al.*, 2001; Wang *et al.*, 2004).

The exact role PPAR-γ plays in both trophoblast invasion and differentiation has yet to be elucidated with apparently paradoxical functions being described in both rodent and human placentas. Much of the data related to understanding PPAR-γ in humans has resulted from *in vitro* experiments. In terms of rodents, PPAR-γ activation appears to be essential for placental development and specifically trophoblast invasion and differentiation (Barak *et al.*, 1999; Asami-Miyagishi *et al.*, 2004). In contrast, the exact role of PPAR-γ in the human placenta remains controversial as studies have demonstrated that PPAR-γ activation both enhances and inhibits differentiation of cytotrophoblasts (Schaiff *et al.*, 2000; 2006). Moreover, while PPAR-γ activation has been shown to induce the differentiation of trophoblasts into syncytiotrophoblasts, activation of this receptor has also been shown to hamper cytotrophoblast invasion while PPAR-γ antagonists have been shown to enhance this process (Tarrade *et al.*, 2001; Handschuh *et al.*, 2006). Although PPAR-γ appears essential for placentation, some studies have demonstrated that PPAR-γ ligands reduce the production of VEGF, which is essential for placental vascularization (Peeters *et al.*, 2005). Furthermore,

recent evidence has shown that overactivation of PPAR-γ at the maternal–fetal interface impaired implantation and placentation and therefore embryonic development (Fournier *et al.*, 2011).

Data has demonstrated that homozygous PPAR-γ-deficient mice embryos die due to placental dysfunction (Kubota *et al.*, 1999). In particular, it appears that ablation of the PPAR-γ gene induces a disruption in both the terminal differentiation of the trophoblast and placental vascularization, leading to severe myocardial thinning and death. Furthermore, these PPAR-γ-null placentas develop a malformed labyrinth zone, with no permeation of fetal blood vessels and dilation and rupture of maternal blood sinuses. In addition, labyrinthine trophoblasts fail to properly differentiate and spongiotrophoblasts abnormally phagocytose maternal red blood cells (Barak *et al.*, 1999). The myocardial thinning that occurs in PPAR-γ-null embryos can be circumvented by the use of tetraploid chimeras. This rescue was only partial with 2 of 5 mutants rescued by 12.5 days of gestation; 1 of 10 by 16.5 days and 1 of 6 at birth (Barak *et al.*, 1999). A recent study has subsequently shown that an epiblastic-specific deletion of PPAR-γ in the placenta was sufficient to rescue the embryonic lethality of PPAR-$\gamma^{-/-}$ zygotes (Nadra *et al.*, 2010). This demonstrates that the likely lethality associated with the PPAR-$\gamma^{-/-}$ embryos, occurs as a result of a placental defect.

In PPAR-γ-null embryos, which were rescued to term, there was no visible white adipose tissue and the embryos possessed a fatty liver emphasising the importance of PPAR-γ in adipogenesis (Barak *et al.*, 1999). This was further emphasized by *in vitro* work demonstrating that embryonic stem cells lacking PPAR-γ were unable to differentiate into adipocytes (Rosen *et al.*, 1999). Several co-activators of PPAR-γ including PBP/DRIP205/TRAP220 and RAP250/PRIP, may also be necessary for placental development. Mice with mutations in these proteins exhibit placental phenotypes that resemble aspects of PPAR-γ-null mice (Zhu *et al.*, 2000; 2003; Antonson *et al.*, 2003). More recently, the mucin gene (*Muc1*) has emerged as a target gene for PPAR-γ in trophoblast development in mice and also as a measure of trophoblast downstream activity of PPAR-γ (Shalom-Barak *et al.*, 2004). In the placenta, *Muc1* protein is localized on the labyrinthine trophoblast around maternal blood sinuses. More importantly, *Muc1* appears to be the only direct target for PPAR-γ, and it appears to be independent of lipid and energy metabolism pathways.

PPAR-γ and pregnancy-specific diseases

PPAR-γ plays a predominant role in normal vascular function (Beyer *et al.*, 2008) and in the differentiation of labyrinthine trophoblast lineages (Schaiff *et al.*, 2000), which along with the fetal endothelium forms the vascular exchange interface with maternal blood essential for the progression of a healthy pregnancy (Parast *et al.*, 2009). More recently, accumulating evidence has suggested that aberrations in PPAR-γ expression and/or function contribute at least in part to a variety of pathophysiological states associated with complicated pregnancies (summarized in Table 1.). In particular, with regard to preterm birth, recent evidence has suggested that this may be linked to a genetic susceptibility factor. In a study conducted by Meirhaeghe *et al.* (2007) in a cohort of patients in Northern Ireland, it was found that there may be a link between PPAR-γ and susceptibility to preterm birth (Meirhaeghe *et al.*, 2007). The PPAR-γ polymorphism, $Pro^{12}Ala$, could potentially influence the duration of gestation and in addition birth weight, implicating an important role for PPAR-γ in genetic susceptibility to preterm birth. Furthermore, the above polymorphism could act as a potential biomarker for preterm birth and be possibly used in the early detection of the condition.

Pre-eclampsia

A reduction in the placental expression of PPAR-γ activators has been demonstrated in some women who develop severe

Table 1

Complicated pregnancy-related conditions and associated PPAR-γ effects

Condition	Associated effect on PPAR-γ	Species	Reference
Pre-eclampsia	↑ DNA binding activity of PPAR –γ	Rat	Crews *et al.*, 2000
Pre-eclampsia	↓ circulating activators of PPAR-γ and ↓ placental expression of PPAR-γ	Human	Waite *et al.*, 2005
Pre-eclampsia	↓ placental expression of PPAR-γ	Rat	Mattace Raso *et al.*, 2008
Pre-eclampsia	Pharmacological antagonism of PPAR-γ	Rat	McCarthy *et al.*, 2011a
Intrauterine growth restriction	↓ fetal lung expression of PPAR-γ	Rat	Joss-Moore *et al.*, 2010
Restricted embryonic development	Over-activation of PPAR-γ	Human	Fournier *et al.*, 2011
Embryonic lethality	Homozygous deletion of PPAR-γ gene	Mouse	Barak *et al.*, 1999; Kubota *et al.*, 1999
Embryonic lethality	Mutations of PPAR-γ cofactors (PBP/DRIP205/TRAP220 and RAP250/PRIP)	Mouse	Antonson *et al.*, 2003; Zhu *et al.*, 2000; Zhu *et al.*, 2003
Preterm birth	Presence of PPAR-γ polymorphism (Pro12Ala)	Human	Meirhaeghe *et al.*, 2007
Gestational diabetes mellitus	Presence of PPAR-γ polymorphisms (Pro12Ala and C 1431 T)	Human	Heude *et al.*, 2011

pre-clampsia (Waite *et al.*, 2005), and significantly higher PPAR-γ DNA binding activity has been demonstrated in placentas from women with both IUGR and pre-eclampsia (Crews *et al.*, 2000). In spontaneously hypertensive rats, there is reduced protein expression of placental PPAR-γ (Mattace Raso *et al.*, 2008). Waite *et al.* (2005) demonstrated that serum extracts from pregnant women contained PPAR-γ activators, and women with severe early-onset pre-clampsia had significantly reduced circulating PPAR-γ activators compared with serum extracts from healthy pregnant women, suggesting that reduced PPAR-γ activity may contribute to pre-clampsia (Waite *et al.*, 2005). In contrast, Holdsworth-Carson *et al.* (2010) examined placental expression of PPAR-γ and demonstrated that placentas from women with pre-clampsia did not demonstrate any differences in mRNA or protein expression of PPAR-γ compared with healthy controls (Holdsworth-Carson *et al.*, 2010).

In our own work with rodents, we initially investigated the role of PPAR-γ in the progression of rodent pregnancy by administering a PPAR-γ-specific antagonist, T0070907 (from gestational days 11–15) to healthy pregnant rats (McCarthy *et al.*, 2011a). Antagonism of PPAR-γ during pregnancy appeared to adversely affect these rats as they were characterized by hypertension, proteinuria, endothelial dysfunction, fetal growth restriction, platelet hyperaggregability, disturbances in the angiogenic balance (VEGF/soluble fms like tyrosine kinase 1; sFlt-1) and a placental labyrinthine trophoblast that exhibited adaptive angiogenesis, increased cellular proliferation and was less differentiated than those from healthy pregnant rats (McCarthy *et al.*, 2011a). Taken together, these findings suggest a pivotal role for PPAR-γ in the progression of a healthy pregnancy and, in addition, a possible role for this receptor in the pathogenesis of pre-clampsia. To investigate the latter, we carried out a separate study in which we administered a PPAR-γ agonist, rosiglitazone, to pregnant rats that had undergone chronic surgical reduction of uteroplacental perfusion to produce a preeclamptic-like state [reduced uterine perfusion pressure (RUPP) rat model of pre-clampsia] (McCarthy *et al.*, 2011b). RUPP rats were characterized by hypertension, endothelial dysfunction and elevated microalbumin creatinine ratios, all classical hallmarks of pre-clampsia; and rosiglitazone administration ameliorated all of these symptoms, suggesting activation of PPAR-γ as a possible therapeutic intervention for pre-clampsia. Furthermore, the majority of beneficial effects observed following rosiglitazone administration were abrogated in the presence of a heme oxygenase-1 (HO-1) inhibitor, which suggests at least part of the mechanistic pathway involved in the protective effects mediated by PPAR-γ in this animal model of pre-clampsia (McCarthy *et al.*, 2011b).

In relation to the mechanism(s) involved in PPAR-γ-mediated effects in pregnancy, NO may act as one of several possible downstream mediators. While pregnancy is associated with an increase in NO levels, studies have yielded conflicting results as to whether nitrite/nitrate (NOx; metabolites of NO) levels are increased (Smarason *et al.*, 1997; Shaamash *et al.*, 2000), decreased (Var *et al.*, 2003; Aydin *et al.*, 2004) or unchanged (Davidge *et al.*, 1996; Daniel *et al.*, 1998; Conrad *et al.*, 1999) relative to normotensive pregnancies in pre-clampsia. In addition, asymmetric dimethylarginine (ADMA) levels (an endogenous inhibitor of NOS) are increased in pre-clampsia compared with normotensive pregnancies (Fickling *et al.*, 1993; Savvidou *et al.*, 2003). ADMA produces superoxide (SO) rather than NO, augmenting oxidative stress and preventing production of NO from L-arginine, which may account for any observed reductions in NO levels. Activation of PPAR-γ has been shown to both restore NO bioavailability (Sorrentino *et al.*, 2007) and increase NO release from human aortic endothelial cells (Polikandriotis *et al.*, 2005) in addition to decreasing ADMA levels.

Pre-eclampsia is characterized by increased platelet aggregation/activation, which may be due to several NO depletion-related mechanisms. Under physiological conditions, NO inhibits platelet aggregation (Loscalzo, 2001); thus, in pathophysiological situations characterized by reduced NO bioavailability, this inhibitory effect would be attenuated considerably. Furthermore, increasing concentrations of ADMA augments platelet aggregation, most likely as a consequence of reduced NO production (Brunini *et al.*, 2006), and peroxynitrite (albeit at high concentrations) has been shown to activate platelets, thus increasing platelet aggregation (Brown *et al.*, 1998). Activated platelets (which express PPAR-γ) act as a major source of reactive oxygen species (ROS) in several pathological conditions (myocardial ischaemia, diabetes and atherosclerosis) and therefore may contribute considerably to the oxidative stress associated with pre-clampsia.

Gestational diabetes mellitus

Gestational diabetes mellitus has been a disease of increasing prevalence in recent years. This disease is characterized by impaired glucose tolerance during pregnancy, affecting 2–8% of all pregnancies (Arck *et al.*, 2010), a figure that has risen by 50% in the last 20 years (Ferrara, 2007). Along with other complications, gestational diabetes mellitus can result in the development of type II diabetes mellitus in both mother and child. PPAR-γ is a major regulator of both glucose and lipid metabolism through its involvement in the regulation of adipogenesis and intracellular insulin signalling processes that ultimately controls glucose homeostasis (Tontonoz *et al.*, 1994). In gestational diabetes, PPAR-γ expression is often dysregulated, leading to changes in insulin sensitivity profiles (Arck *et al.*, 2010). Furthermore, a recent study has suggested that the PPAR-γ variants, $Pro^{12}Ala$ and C1431T, and their haplotypes may play a role in the susceptibility of developing gestational diabetes (Heude *et al.*, 2011), further demonstrating their potential as biomarkers for disease and possible therapeutic targets for translational medicine.

IUGR

IUGR is a disease characterized by poor fetal growth during pregnancy, resulting in low birth weight and often preterm delivery (Lawn *et al.*, 2005). Additionally, IUGR is often associated with altered lung development in both humans and rat models (Joss-Moore *et al.*, 2010). IUGR has a similar placental pathology to pre-clampsia, but there is no exaggerated dyslipidaemia or hypertension (Rodie *et al.*, 2005). PPAR-γ is thought to have a role in fetal lung development via its direct regulation of chromatin-modifying enzymes such as Setd8. In a study carried out by Joss-Moore *et al.*

(2010), it was shown that lung PPAR-γ expression was reduced by IUGR in both male and female neonatal rats, and this reduction was associated with a decrease in Setd8. This could suggest that down-regulation of PPAR-γ may significantly contribute to abnormal fetal lung development associated with IUGR.

PPAR-γ as a therapeutic target

PPAR-γ activation has been shown to play a key role in metabolic processes related to cell differentiation, proliferation and lipid metabolism; and, as a consequence, substantial emphasis has been placed on elucidating the mechanisms involved in its activation due to the potential for its use as a pharmacological target for the treatment of pathophysiological metabolic syndromes such as type II diabetes, atherosclerosis and obesity. Thiazolidinediones such as rosiglitazone activate PPAR-γ in order to improve insulin sensitivity profile; however, the thiazolidinediones currently on the market are first-generation, nonspecific agonists of PPAR-γ, resulting in the deleterious side effects (Kung and Henry, 2012) that have caused their limited usage and in some cases have been withdrawn from the market (Mutalik, 2011). While there has yet to be an assessment of the risks associated with thiazolidinedione administration during pregnancy and a safety profile remains to be established (Arck *et al.*, 2010), there is hope on the horizon in terms of modulators of PPAR-γ activity. The new development of highly targeted selective PPAR-γ modulators (SPPARγMs) and dual PPAR-γ/PPAR-α agonists (Kung and Henry, 2012) has led to the re-emergence of PPAR-γ as a potential therapeutic target.

Anti-inflammatory effects of PPAR-γ

A beneficial role for PPAR-γ in conditions associated with an inflammatory response, such as IUGR, preterm labour and spontaneous abortion (Challis *et al.*, 2009), has been suggested on the basis of its numerous anti-inflammatory effects (Marx *et al.*, 2000; Pasceri *et al.*, 2000; Verrier *et al.*, 2004; Sasaki *et al.*, 2005). PPAR-γ activation has been shown to prevent microparticle (plasma membrane vesicles with procoagulant and pro-inflammatory properties) induced vascular hypo-reactivity through the regulation of pro-inflammatory proteins. In particular, ligand-induced activation of PPAR-γ attenuated the microparticle-mediated up-regulation of NF-κB transcription, expression and activation, which ultimately prevented increases in both interleukin (IL)-6 and IL-8 (Tesse *et al.*, 2008). In both monocytes and macrophages, PPAR-γ activation has been shown to reduce the production of cytokines including TNF-α (Hofmann *et al.*, 1994), IL-1β and IL-6 via the inhibition of pro-inflammatory transcription factors such as AP-1, STAT and NF-κB (see Figure 1; Jiang *et al.* 1998; Ricote *et al.* 1998; Barak *et al.* 2002; Matsumoto *et al.* 2008). Furthermore, PPAR-γ activation suppresses the expression of pro-inflammatory adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin (Wang *et al.*, 2002), which would reduce the increase in adherence of monocytes to both endothelial and polymorphonuclear cells (Imamoto *et al.*, 2004). Zhang *et al.* (2012) demonstrated that PPAR-γ and PPAR-α act as regulators of IFNγ and IL-17α production by human T cells in a sex-specific way. In mice where androgen levels were elevated, PPAR-α levels were increased, and levels of PPAR-γ were decreased. In some pregnancies, androgen levels are raised, such as in the patients suffering from polycystic ovary syndrome, which can be a risk factor in the development of pre-clampsia (Roos *et al.*, 2011). Similarly, platelets express PPAR-γ and activation of this receptor can inhibit the pro-inflammatory effects of platelets, inhibiting both platelet aggregation and the release of both thromboxane A2 (TXA2) and adenosine triphosphate from platelets reducing the generation of further mediators associated with the syndrome of pre-clampsia (Akbiyik *et al.*, 2004). This could additionally serve as a therapeutic target for autoimmune disease and could serve a further cardioprotective and vasculoprotective role in the prevention of clot formation for patients at risk of recurrent stroke.

As pre-clampsia is thought to have an underlying autoimmune component (Xia and Kellems, 2009; Biggar *et al.*, 2010), targeting PPAR-γ pharmacologically could serve to ameliorate the autoimmune response and potentially act to prevent the inception of the disease in genetically susceptible individuals. Additionally, this could also serve as a future pharmacological target for severe cases of autoimmune disease such as pemphigus vulgaris, rheumatoid arthritis and Crohn's disease.

In the vasculature, PPAR-γ activation leads to inhibition of endothelial inflammation via the suppression of key pro-inflammatory gene expression that is NF-κB. PPAR-γ is expressed by both endothelial cells where it appears to play an important role in the regulation of diet induced hypertension (Nicol *et al.*, 2005) and vascular smooth muscle cells where PPAR-γ activation inhibits cell proliferation and migration while promoting apoptosis. In addition, PPAR-γ activation inhibits NO overproduction, IL-6 and TNF-α expression, and suppresses COX-2 and iNOS induction via the suppression of NF-κB and activator protein-1 activation (Inoue *et al.*, 2000; Maggi *et al.*, 2000).

Vasculoprotective effects of PPAR-γ

Endothelial dysfunction plays a vital role in the pathophysiology of many conditions, including hypertension, stroke, atherosclerosis, hypercholesterolaemia and diabetes (Cai and Harrison, 2000; Kobayashi *et al.*, 2000; 2004; 2005; Landmesser *et al.*, 2004; Matsumoto *et al.*, 2007). In several of these pathophysiological cardiovascular conditions, activation of PPAR-γ restores vascular structure and corrects endothelial dysfunction (Walcher and Marx, 2004; Schiffrin, 2005; Li and Palinski, 2006; Cao *et al.*, 2007). In particular, PPAR-γ agonists improve endothelium dependent vasodilatation and also reduce the elevated blood pressure associated with a number of hypertensive conditions (Kaufman *et al.*, 1995; Caballero *et al.*, 2003; Forst *et al.*, 2005), including pre-eclampsia (McCarthy *et al.*, 2011b). PPAR-γ mediates its vasculoprotective effects via several mechanisms, including the suppression of the pro-inflammatory cytokine, TNF-α, in type II diabetics (Pistrosch *et al.*, 2004; Horio *et al.*, 2005; Sourij *et al.*, 2006) and the attenuation of endothelin-1 (ET-1) levels in an animal model of diabetes (Kanie *et al.*, 2003). In terms of the latter pathway, chronic administration of a PPAR-γ agonist to streptozotocin diabetic rats normalized both

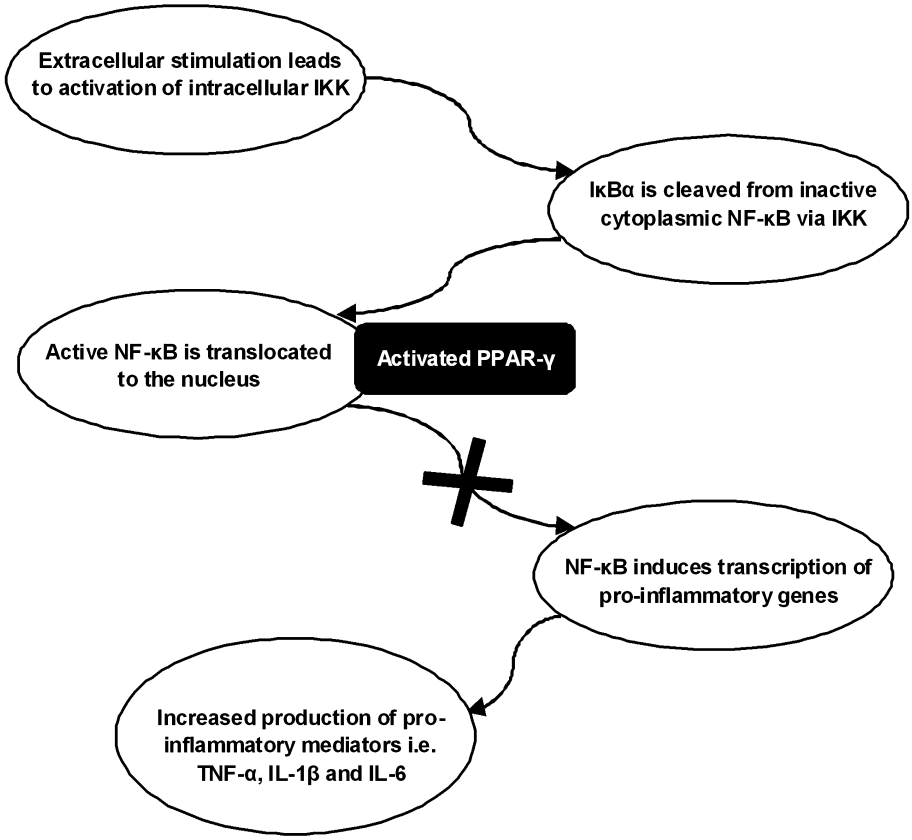

Figure 1

Anti-inflammatory effects of PPAR-γ via NF-κB transrepression (adapted from Li and Yang, 2011). In the transcriptional control of inflammation, pro-inflammatory cytokines act on membrane bound receptors to induce the activation of the enzyme IκB kinase (IKK). IKK then phosphorylates the IκBα protein bound to the inactive cytosolic NF-κB, leading to the dissociation of the two dimers and activation of NF-κB. The activated NF-κB is then translocated to the nucleus where it induces the transcription of a number of pro-inflammatory genes, leading to an increase in cytokine (TNF-α, IL-1β & IL-6 etc.) production. Following the binding of a ligand to PPAR-γ, the latter prevents the recruitment of transcriptionally active NF-κB, leading to inhibition of inflammatory gene expression and a resultant anti-inflammatory effect.

mRNA for prepro-ET-1 and the plasma concentrations of ET-1 via the inhibition of the AP-1 pathway (Delerive *et al.*, 1999a,b; Satoh *et al.*, 1999).

In addition to their endothelial-stabilizing effects, PPAR-γ agonists may also restore the balance of angiogenic factors in pre-eclampsia, as this condition is characterized by a significant increase in the anti-angiogenic molecule, sFlt-1 (Ahmad and Ahmed, 2004). PPAR-γ agonists have been shown to up-regulate HO-1 expression an anti-oxidant enzyme that negatively regulates the production of the anti-angiogenic mediator, sFlt-1 (Cudmore *et al.*, 2007; Kronke *et al.*, 2007). Moreover PPAR-γ agonists serve to increase the production of the pro-angiogenic hormone, VEGF, in macrophages, vascular smooth muscle cells and endothelial cells (Jozkowicz *et al.*, 2000; Yamakawa *et al.*, 2000; Inoue *et al.*, 2001a,b; Negro *et al.*, 2005; Suwaki *et al.*, 2007).

As mentioned previously, activation of PPAR-γ has been shown to restore NO bioavailability via the inhibition of SO production by NADPH oxidase in endothelial progenitor cells from patients with type II diabetes (Sorrentino *et al.*, 2007). Furthermore, PPAR-γ ligands increase NO release from porcine and human aortic endothelial cells (Martens *et al.*, 2002; Polikandriotis *et al.*, 2005) and decrease ADMA levels, all of which improves NO bioavailability (Cho *et al.*, 2004; Polikandriotis *et al.*, 2005; Goya *et al.*, 2006; Wang *et al.*, 2006). These findings provide further evidence that PPAR-γ agonists have the potential both to induce direct modification of endothelial cell function and to modulate the production of NO, a critical mediator in the maintenance of normal vascular physiology and in the pathogenesis of pre-clampsia.

Effect of PPAR-γ activation on fetal development and preterm birth

In the case of IUGR, PPAR-γ may equally serve as a potential drug target as in the case of pre-clampsia. As mentioned earlier, Joss-Moore *et al.* (2010) demonstrated that abnormal lung development in IUGR may be linked to a decrease in PPAR-γ expression. Moreover, the adverse effects associated with this decrease in PPAR-γ expression were ameliorated in neonatal IUGR rat offspring by the administration of maternal docosahexanoic acid (DHA), an endogenous PPAR-γ activator. This suggests a potential supplementary role for maternal DHA, dietary DHA and/or synthetic DHA in the treatment of IUGR. Furthermore, this could also indicate another therapeutic avenue for future PPAR-γ-targeted treatments.

PPAR-γ may also prove to be effective as a drug target for patients at risk for preterm birth. It has been suggested that the aforementioned PPAR-γ polymorphism Pro[12]Ala may represent a genetic susceptibility factor to low birth weight and preterm labour (Meirhaeghe *et al.*, 2007). In targeting Pro[12]Ala with an exact PPAR-γ antagonist for this polymorphism, this could serve to reduce the risk of preterm birth in genetically susceptible individuals. Similarly, in the case of gestational diabetes, by targeting the Pro[12]Ala and C1431T variants of PPAR-γ in this manner, PPAR-γ could be exploited to serve a protective role for genetically susceptible individuals to gestational diabetes.

Conclusion

As discussed above, the applications of PPAR-γ as a pharmacological target are numerous, serving a wide range of functions, not just in the aetiology and treatment of pre-clampsia but also across a range of other cardiovascular, neurological, autoimmune and metastatic diseases. As of yet, there have been no pharmacological developments in PPAR-γ-targeted drug treatments for pre-clampsia, however, as a future drug target for this disease, PPAR-γ holds promise. In recent years, there has been increased interest in this area of research and new novel PPAR-γ agonists are under development to replace the 'dying' drug class that is the glitazones. The majority of these are aimed at the improvement of insulin sensitivity and metabolic profile (Cho *et al.*, 2011; Chaudhary *et al.*, 2012; Rikimaru *et al.*, 2012); however, the aims of this research area could similarly be applied to the development of a drug geared towards the prevention and treatment of pre-clampsia and other adverse pregnancy outcomes, such as in the treatment of neonatal hyperoxia-induced lung injury for which rosiglitazone may serve a protective role (Cai and Xu, 2012). As yet, it is unknown whether PPAR-γ agonists are toxic to the embryo and/or possess teratogenic effects; thus, caution must be exercised in the extrapolation of any data from experimental models to the clinical situation. While previous studies have demonstrated cardioprotective effects of rosiglitazone in an experimental model of myocardial ischaemia/reperfusion injury (Yue *et al.*, 2005; Molavi *et al.*, 2006; Gonon *et al.*, 2007), concern has been expressed regarding the safety profile of this glitazone as reports linking it with a major risk of death from cardiovascular causes have also emerged (Home *et al.*, 2007; Krall, 2007; Nissen and Wolski, 2007; Dluhy and McMahon, 2008). Therefore, it is essential that appropriate teratogenicity studies in animals be carried out as part of any investigation into the therapeutic potential of PPAR-γ agonists in complicated pregnancies. Finally, PPAR-γ is rapidly becoming an exciting new area for pharmacological research, its potential for physiological benefit encompassing a vast range of pathological disease states, but it is its potential for the treatment of pre-clampsia and other adverse pregnancy conditions that is perhaps the most intriguing. As there is no current treatment for pre-clampsia other than delivery of the baby, which can pose significant risks for the developing fetus depending on the severity of the disease and period when diagnosed, this makes PPAR-γ's potential for therapeutic benefit all the more poignant. Thus far, there has been little investigation into the use of PPAR-γ as a possible pharmacological target for the treatment and prevention of pre-clampsia. In the face of mounting evidence supporting a role for PPAR-γ in the pathogenesis of pre-clampsia, it seems pertinent to explore this avenue of prospective treatment for expectant mothers everywhere.

Conflicts of interest

None.

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