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Role of Nuclear Receptors Peroxisome Proliferator-Activated Receptors (PPARs) and Liver X Receptors (LXRs) in the Human Placental Pathophysiology

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1. Introduction

The placenta is a transitory structure indispensable for the proper development of the embryo and fetus during mammalian gestation. Like other members of the nuclear receptor family, the peroxisome proliferator-activated receptors (PPARs) and the liver X receptors (LXRs) are known to be involved in the physiological and pathological events occurring during the placentation. This placental involvement has been recently confirmed focusing on the early stages of placental development (implantation and invasion....), mouse knockout phenotypes and cyto/syncytio-trophoblastic physiology. In this review, we describe the involvement of PPARs and LXRs in placenta and in the amniotic membrane during gestation (e.g., fat transport and metabolism...), in pathological process (e.g., chorioamnionitis, preeclampsia...), metabolic disorders (e.g., diabetes) and parturition.

2. The peroxisome proliferator-activated receptors (PPARs)

Discovered in 1990, PPARs are known for their biological role in inducing the proliferation of peroxisomes in rodents (Issemann & Green, 1990). They are transcription factors belonging to the ligand-activated nuclear hormone receptor superfamily (Michalik et al., 2002) and have been identified in different species such as the xenopus, mouse, rat, and humans.

2.1 Nomenclature and structure of PPARs

In all these species, PPARs present three isotypes encoded by distinct single-copy genes: PPARα (NR1C1), PPARβ/δ (also called NUC1 or NR1C2), and PPARγ (NR1C3), located on chromosomes 22, 6, 3 in humans. The PPARγ gene alternative promoters give rise to three different isoforms named γ1, γ2, and γ3 which differ at their 5_ends (Fajas et al., 1997). PPAR α, β, γ1/γ3, γ2 translation produces proteins of 468, 441, 475, and 505 amino acids, respectively, with a molecular weight of 49 to 56 kDa (Fournier et al., 2007). By performing multiple PPAR nucleotide/protein alignments in different species, a strong interspecies identity (human, mouse, rat, bovine, ≈84%) has been established, illustrating a strong evolutionary conservation among species by derivation from a common ancestor (Table 1).

Like several other members of the nuclear receptor superfamily, PPARs possess the typical structure organized in six domains named A to F (Figure 1) (Escher et al., 2000). Domain C (DBD: DNA binding domain) contains two zinc fingers and allows promoter target genes interaction and dimerization with its preferential nuclear receptor: retinoid X receptor (RXR). The PPAR/RXR heterodimer binds to the target gene promoter response element named peroxisome proliferator response element (PPRE) which is made up of two half site AGGTCA separated by one or two nucleotides (also called DR1 or DR2 for direct repeat 1 or 2). Domain E/F allows ligand binding and contains a ligand-dependent transactivation function called AF2 (activating function 2). It is also involved in dimerization and interaction with cofactors.

		cDNA homology (%)			Protein homology (%)		
		Mouse	Rat	Bovine	Mouse	Rat	Bovine
Human relative identity percent	PPARα	44	64	72	92	92	94
	PPARβ	60	69	75	92	91	95
	PPARγ1	79	84	78	98	97	97
	PPARγ2	86	86	88	96	95	95

Table 1. Percentage of nucleotide and amino acid identity between human and mouse, rat and bovine PPAR sequences respectively. No PPARγ3 alignment was carried out owing to lack of data on different species. The different sequences came from Ensembl and were aligned with Genomatix software (Borel et al., 2008).

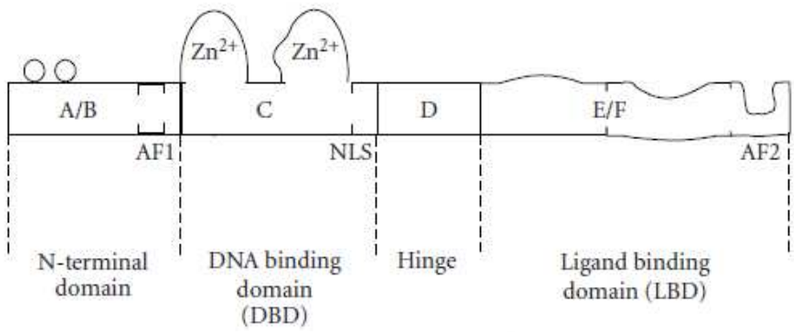

Fig. 1. Schematic representation of typical nuclear receptor structure. AF1: activating function 1 (ligand-independent function), AF2: activating function 2 (ligand-dependent function), NLS: nuclear signal localization (Borel et al., 2008).

2.2 PPAR ligands

As with the other nuclear receptors, the binding of the ligand is a key step in the control of PPAR transcriptional activity. In the absence of a ligand, corepressors and histone deacetylases (HDAC) bind to PPARs and inhibit the transcription of target genes. PPAR ligands have the ability to dissociate the corepressor complexes from the PPAR/RXR heterodimer, allowing the binding of the coactivators in order to initiate and activate transcription. There are two kinds of ligands for the PPARs: natural and synthetic. Among the natural ligands the monounsaturated fatty acids (FA) (e.g., oleic acid) and the polyunsaturated fatty acids (PUFA) (e.g., linoleic acid, linolenic acid and arachidonic acid) are described as ligands for PPAR*a*, PPARβ and PPARγ. They act with concentrations

consistent with those found in human serum (Desvergne & Wahli, 1999). The different PUFA metabolites: 8(S)- and 15-hydroxyeicosatetraenoic acid (8(S)- and 15-HETE), leukotriene B4 (LTB4), 9- and 13- hydroxyoctadedienoic acid (9-HODE and 13-HODE) and 15-deoxy-Δ12,14-prostaglandin J2 (PGJ2) are potent selective activators of PPAR*a* and PPARγ.

More recently, it has been demonstrated that P450 eicosanoids are potent PPAR*a* and PPARγ ligands (Ng et al., 2007). These ligands induce PPAR binding to PPRE and can modify the expression of PPARα responsive genes like apoA-I or apoA-II in the same way than synthetic ligands. Thus the finely regulated conversion of PUFAs to eicosanoids through either the lipoxygenase, cyclooxygenase, or cytochrome P450 monooxygenase pathways may provide a mechanism for the differential regulation of PPAR*a* and PPARγ and their respective target genes. PPARβ can be activated by different types of eicosanoids including prostaglandinA1 (PGA1) and prostaglandin D2 (PGD2). Many synthetic ligands exist and have been used in PPAR work. These ligands include prostaglandin 12 analogs, pirinixic acid (Wy-14643) for PPAR*a*, hypolipidemic and hypoglycemic agents (nonthiazolidinedione) for PPARβ, and thiazolidinediones (e.g., rosiglitasone, troglitazone) for PPARγ (Michalik et al., 2002).

2.3 Placental PPAR expression patterns

The three PPAR isoforms are been shown to be expressed in the villous trophoblastic cells and syncytiotrophoblasts of the human term placenta (Fournier et al., 2007). Furthermore, the three PPARs are present in total placenta, amnion, chorion, and in amnion-derived WISH epithelial cell line at the mRNA and protein levels. But the expression of PPAR*a* and PPARγ seems to be weaker than that observed for PPARβ/δ. In addition, PPARγ is more express in chorion than in amnion (Borel et al., 2008).

2.4 Implications of PPARs in placenta and fetal membranes

2.4.1 Placental and amniotic presence of PPARs ligands

The lipids of human amnion and chorion are enriched in the essential fatty acid arachidonic acid, which is the precursor of all the prostaglandins of the 2 series (Schwarz et al., 1975). Sixty-six percent of the arachidonic acid of the human fetal membranes are available in the glycerophospholipids of these tissues and can easily be converted into PGD2 (Okita et al., 1982). The placenta produces considerable amounts of PGD2 (Mitchell et al., 1982). The enzymes necessary to convert PGD2 into prostaglandin J2 (PGJ2) are present and co expressed with PPARγ in placenta. 15 Deoxy-Δ12,14-PGJ2 (15dPGJ2) and its precursor PGD2 are present in amniotic fluid at concentrations that do not exceed 3 nM (Helliwell et al., 2006). However, this amniotic fluid concentration cannot be an exact representation of the physiological placental reality for PPARs ligands because the nuclear concentration is not measured. The maternal blood may also be a source of PPAR ligands for the human placenta and the fetal membranes. It has been established that a heatstable compound (not a protein, but rather a prostanoid or a fatty acid) is detected in maternal blood serum and is able to activate the PPARγ (Waite et al., 2000). The presence of classical and new PPARs ligands (e.g., P450 eicosanoids, PUFA metabolites) in placenta and fetal membranes suggests that they could activate PPAR, induce PPAR binding to PPREs and modify the expression of PPAR target genes.

2.4.2 Fundamental implications of PPARs during early placentation

As a determining result, the knockout of the PPARγ in mice (Barak et al., 1999) yielded the first findings indicating the importance of this factor in early embryonic and perinatal development. These results are concomitant with those obtained by the generation of RXRa or β null mice (PPARγ partner in the functional heterodimer), also showing an embryonic lethality explained by the lack of generation of a functional labyrinthine zone (Sapin et al., 2001; Parrast et al., 2009). Furthermore, complementary studies conducted by the inactivation of PPARγ coactivators or coregulators, such as peroxisome proliferators activator receptor-binding protein (PBP) and peroxisome proliferator-activated receptor-interacting protein (PRIP), also lead to severe placental dysfunction, such as inadequate vascularisation of the structure (Antonson et al., 2003; Zhu et al., 2000; Zhu et al., 2003). Furthermore, the inactivation of PPARβ/δ led to the formation of abnormal gaps and a thinner but fully differentiated vascular structure in the placentodecidual interface (Barak et al., 2002). These results establish the no redundant roles of PPARγ and PPARβ/δ in early mouse placental development. Recent analysis of PPARγ null mice also demonstrated that PPARγ plays a pivotal role in controlling placental vascular proliferation and contributes to its termination in late pregnancy [Nadra et al., 2010]. In human, PPARβ/δ plays a central role at various stages of pregnancy like implantation, decidualization, and placentation (Wang et al., 2007). By contrast, the inactivation of PPARa has no effect on placental formation or on the developing fetus and by the way theirs possible roles during pregnancy had to be clarified (Michalik et al., 2002). In humans, the studies are almost exclusively focused on the PPARγ roles during early placentation. It has been clearly established that all three PPARs can stimulate or inhibit the differentiation and/or proliferation of the villous cytotrophoblasts into syncytiotrophoblasts and the synthesis of chorionic gonadotrophic hormone and may hamper extravillous trophoblastic cell invasion (Fournier et al., 2007). It's also clearly established that hCG gene expression is differentially regulated in the villous and extra-villous trophoblast lineages during their in vitro differentiation and modulated in an opposite way by PPARγ (Handschuh et al., 2009).

2.4.3 Roles of PPARs in the uptake and transport of trophoblastic lipids

As one of the first functions described for PPARγ in other tissues, trophoblastic lipid uptake and accumulation are also regulated in part by this factor (Schaiff et al., 2007). The PPARγ ligands seem to increase the uptake and accumulation of the fatty acids in human placenta (Schaiff et al., 2005). This regulation is associated with an enhanced expression of adipophilin (fat droplet-associated protein) and fatty acid transport proteins (1 and 4) in human trophoblasts (Schaiff et al., 2005; Bildirici et al., 2003; Duttaroy, 2004). These results were confirmed by the *in vivo* activation of PPARγ by its agonist rosiglitazone in mice, which also leads to the enhancement of the previous described genes plus two new ones involved in the lipid transport: S3-12 (plasma associated protein) and myocardial lipid droplet protein/MLDP (Schaiff et al., 2007). Taken together, these results confirm the results obtained on PPARγ-null mutants: the absence of the lipid droplets normally present around the fetal vessels in the wild-type placenta (Barak et al., 1999).

2.4.4 PPARs in placental inflammatory response and in the parturition signaling

At this stage of our knowledge of PPARs, the most interesting results have been obtained with the study of their involvement in the inflammation process, which may be linked to

labor at term and also to the premature rupture of fetal membranes (Figure 2). Term labor is associated with an increase in proinflammatory proteins and cytokines such as IL1β, IL6, IL8, IL10, and TNF-a. This increase in proinflammatory proteins and cytokines induces uterine contractions. PPARγ ligands have been demonstrated to inhibit the secretion of IL6, IL8, and TNF-a in amnion and chorion (Lappas et al., 2006), highlighting the role of PPARs in the regulation of the inflammatory response in human gestational tissues and cells (Kniss, 1999; Lappas et al., 2002; Ackerman et al., 2005; Berry et al., 2005). The parathyroid hormone-related protein (presenting a cytokine-like action) is involved in many processes during normal and pathological pregnancies, and is decreased by PPARγ stimulation (Lappas & Rice, 2004), which also blocks proinflammatory cytokine release by adiponectin and leptin (Lappas et al., 2005). The production of prostaglandins by the endometrium, the myometrium, and the fetal membranes induces the contraction of the myometrium during labor. This generation of uterotonic prostaglandins correlates with the increased prostaglandin-endoperoxide synthase type 2/cyclooxygenase type 2 (COX-2) activity and the increased secretory phospholipase A2-IIA (sPLA2) mRNA, proteins and activities. By inhibiting the production of the COX-2 and sPLA2 in fetal membranes, PPARγ promotes the quiescence of the uterus during gestation (Ackerman et al., 2005). The PPARγ level of expression remains stable throughout gestation, except for the period just before labor, when its expression in fetal membranes declines. This reduction is coincidental with a

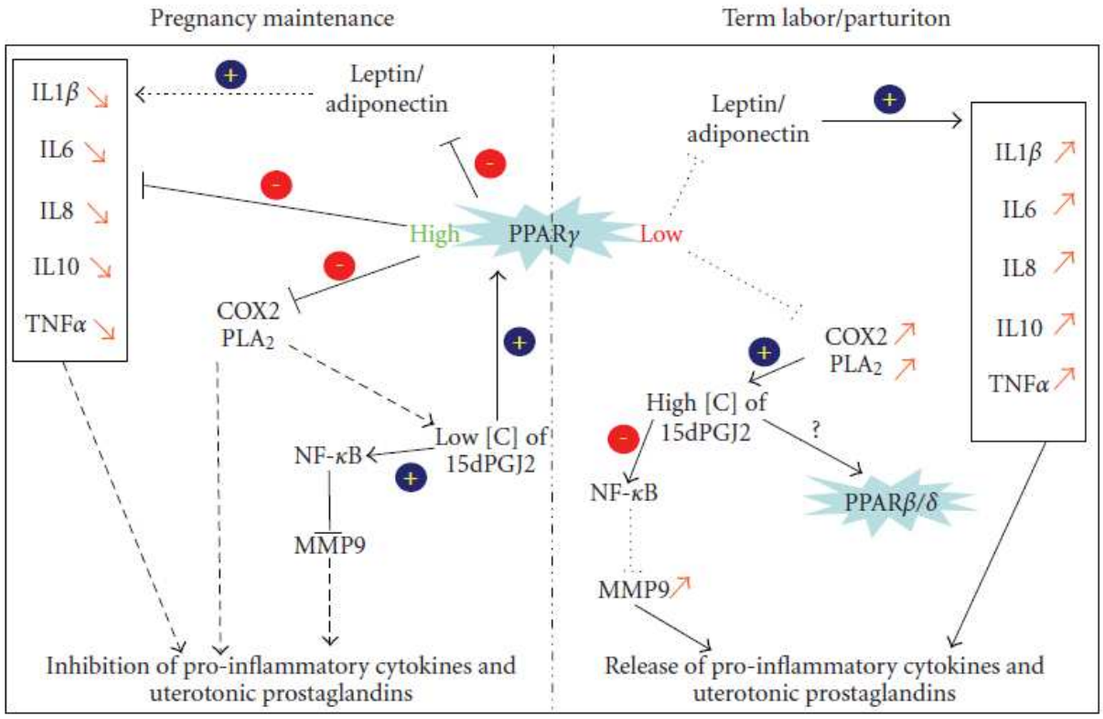

Fig. 2. Schematic representation of PPARγ implication in pregnancy maintenance and labor. IL1β: Interleukin 1β; IL6: Interleukin 6; IL8: Interleukin 8; IL10: Interleukin 10, TNFa: Tumor Necrosis Factor a; COX2: Cyclo-oxygenase type 2; PLA2: Phospholipase A2; NF-κB: Nuclear Factor-Kappa B; MMP9: Matrix Metalloproteinase 9; 15dPGJ2: 15-Deoxy-Δ12, 14 prostaglandin J2 (Borel et al., 2008).

relative increase in COX-2 expression (Dunn-Albanese et al., 2004). The PPAR action seems to be concentration-dependent. A small amount of 15dPGJ2 (<0.1 μM) acts through the PPARγ signaling pathway, where at high concentration (1 μM) its actions are most probably mediated through other pathways: PPARβ/δ and/or an inhibition of NF-κB independent of PPARs (Berry et al., 2005). Furthermore, 15dPGJ2 and troglitazone were also demonstrated to have some anti-inflammatory or apoptosis-induction specific effects by PPARγ-independent pathways (Lappas et al., 2006).

2.4.5 PPARs in placental and amniotic membranes pathologies

In contrast to the different roles described for PPARs during human placentation, only a few studies on PPARs and placental pathologies have been conducted. PPARs may be involved in the pathophysiology of gestational diabetes mellitus, intrauterine growth restriction and preeclampsia (Holdsworth-Carson et al., 2010). In choriocarcinoma and hydatiform moles, a downregulation of the PPARγ expression is observed but this real influence needs to be elucidated (Capparuccia et al., 2002). The potential involvement of PPARγ on preeclampsia is suggested by the fact that this pathology is associated with an increased peroxidation in trophoblasts (Roberts et al., 1999; Ware Branche et al., 1994). An overproduction of 15-HETE has also been noted, suggesting a deregulation of PPARγ (Johnson et al., 1998). This can cause a strong transactivation of PPARγ during early pregnancy, resulting in a reduction of extravillous trophoblastic invasion, one cellular explanation often cited in the physiopathology of preeclampsia (Schild et al., 2002; Fournier et al., 2002; Fournier et al., 2008a). It is also established that deletion of PPARγ, PPARβ/δ, and some of their coactivators (PBP, PRIP, and RAP250) induce abnormal placental phenotypes (abruption, reduction of fetomaternal exchanges, and alterations of trophoblastic differentiation) in null mutants (Barak et al., 1999; Antonson et al., 2003; Zhu et al., 2000; Barak et al., 2002; Kuang et al., 2002; Nadra et al., 2006). Chromosomal and/or genetic alterations (point mutation or deletion) may occur for these genes, inducing human placental alterations. The placental 11β hydroxysteroid dehydrogenase type 2 is a target gene of PPARs (Julan et al., 2005). This enzyme plays a key role in fetal development by controlling fetal exposure to maternal glucocorticoids. An abnormal regulation by PPARs may result in an absence of fetal protection. In the rat placental HRP-1 established cell line, the phthalate and derivatives transactivate PPARs (a and γ) induced an increase in uptake rates of fetal essential fatty acid and the transport of arachidonic and docosahexaenoic acid (Xu et al., 2005). If such a mechanism can be induced by the phthalates during human placentation, this may strongly affect the fetal essential fatty acid content during growth.

Gestational diabetes is linked to impaired lipids metabolism (Capobianco et al., 2003) and the increase of PPARγ observe in human trophoblastic cells culture might be involved in the impairment of placental development induced by high glucose conditions (Suwaki et al., 2007). Decreased 15dPGJ2 in blood of diabetic mothers is also linked to a decrease in placental PPARγ expression. The inhibition of PPARγ results in an induction of a placental proinflammatory environment associated with an increase in nitrogen monoxide production and release, which can impair fetoplacental development (Jawerbaum et al., 2004; Jawerbaum & González, 2006; Jawerbaum & Capobianco , 2011). The PPAR regulation of inflammation may be very important in another obstetrical pathology of the amniotic membranes: the chorioamnionitis. This pathology, usually due to an ascendant colonization

of pathogenic microorganisms from the vagina to the uterus, is closely associated with preterm labor and premature rupture of membranes (chorion and amnion). These ruptures of membranes seem to arise from deregulated proinflammatory factor synthesis. It has already been reported in this pathology that IL1*β*, IL6, IL8, TNF-*a*, and prostaglandinE(2) show inadequate concentrations in placental membrane and in amniotic fluid (Willi et al., 2002; Zaga et al., 2004; Jacobsson et al., 2005; Zaga-Clavellina et al., 2006). As PPARs may be involved in the occurrence and control of this inflammatory response, further studies are needed to assess their importance in this process and to find new possible therapeutic strategies to prevent this damaging pathology.

More generally, the use of natural and synthetic PPAR ligands looks to be a promising way in preventing placental pathologies such as endometriosis, preeclampsia or diabetes (Giaginis et al., 2008). An interesting study also demonstrates that the reduction of LPS induction of cytokines is reduced by PPAR*γ* ligands in fetal membranes. Nevertheless, the few studies already conducted were done practically only on animal (rodent) models and looks to have positive effects on the pathologies (Toth et al., 2007). Till now, the major problem using, for example, TZD (thiazolidinediones) linking to the PPAR*γ* pathways still the numerous adverse effects of this kind of treatment (e.g., weight gain, anemia, leukopenia, etc.). Perhaps, at the level of clinician actual knowledge, PPAR*γ* and its ligands could be used in a first time, only as good early marker candidates for the diagnosis of pregnancy pathologies like, for example, preeclampsia.

3. The liver x receptor (LXRs)

First discovered and defined as orphan receptors, liver X receptors (LXRs) were subsequently identified as the nuclear receptor target of the cholesterol metabolites, oxysterols (Apfel et al., 1994; Janowski et al., 1996). LXR pathway regulates lipid metabolism and inflammation via both the induction and repression of target genes (Calkin & Tontonoz, 2010) and have been identified in different species such as the vase tunicate, xenopus, zebrafish, mouse, rat, and humans.

3.1 Nomenclature and structure of LXRs

LXR*a* (NR1H3) and LXR*β* (NR1H2) belong to a subclass of the nuclear receptor superfamily, that form obligatory heterodimers with retinoid X receptor (RXR), the receptor of 9-cis retinoic acid. In humans LXR*a* and LXR*β* are encoded by two distinct genes located on chromosomes 11 and 19, respectively. LXR were initially isolated from a human liver cDNA library as orphan receptors. Later, oxysterols, which are oxidized derivatives of cholesterol, were identified as their natural ligands and the first physiological functions were associated with cholesterol homeostasis. By performing multiple LXR nucleotide/protein alignments of LXRs in different species, a strong interspecies identity (human, mouse, rat, bovine, ≈87%) has been established, illustrating a strong evolutionary conservation among species by derivation from a common ancestor (Table 2).

Similar to other nuclear receptors, both LXR isoforms comprise four distinct domains: 1) an amino-terminal activation domain (AF-1), recruiting ligand-independent co-activators (domain A/B), 2) a DNA-binding domain containing two zinc fingers (domain C), 3) a hinge domain, binding co-repressors in absence of ligand (domain D) and 4) a multi-functional

carboxy-terminal domain, required for dimerization, containing a hydrophobic ligand binding site and a transactivation domain (AF-2) recruiting co-activators (domain E/F) (Figure 1). Interestingly, even though both DNA and ligand-binding pockets share 80% identity, human and mouse LXR*β* are shorter than LXR*a* in their N-terminal domain (12 and 11 amino acids, respectively) and longer in the hinge region (23 and 18 amino acids, respectively). This fact could account for the lack of redundancy *in vivo*, even though both LXR isoforms bind similar DNA sequences and ligands *in vitro* (Viennois et al., 2011). LXR *a*, *β*, translation produces proteins of 447, 461 amino acids, respectively, with a molecular weight of 55 kDa for both (Michael et al., 2005). LXR*a* exists in three variants originating from alternative promoter usage and mRNA splicing: LXR*a*1, LXR*a*2, and LXR*a*3 (Chen et al., 2005).

		cDNA homology (%)			Protein homology (%)		
		Mouse	Rat	Bovine	Mouse	Rat	Bovine
Human relative identity percent	LXRα	88	89	91	91	92	92
	LXRβ	87	87	87	81	81	78

Table 2. Percentage of nucleotide and amino acid identity between the human, mouse, rat, and bovine LXR sequences. No LXR *a*1, *a*2 and *a*3 alignment was carried out owing to lack of data on different species. The different sequences came from Ensembl and were aligned with Genomatix software.

3.2 LXR ligands

As with PPARs, there are two kinds of ligands for the LXRs: natural and synthetic. The physiological LXR agonist ligands are oxysterols, oxidized metabolites of cholesterol. In mammals, there are two sources of plasmatic oxysterols, *in vivo* production by enzymatic or chemical pathways, and exogenous nutritional supply (Viennois et al., 2011). Natural activating oxysterols include 22(R) hydroxycholesterol in steroidogenic tissues, 24(S)-hydroxycholesterol in brain and plasma, 24(S),25-epoxycholesterol mainly found in the liver and 27-hydroxycholesterol in macrophages. These oxysterols have been reported to activate both LXR*a* and LXR*β* (Janowski et al., 1996). Likewise, desmosterol, a cholesterol precursor produced from zymosterol, could also activate LXR (Yang et al., 2006). Molecules derived from the bile acid pathway in particular natural 6α-hydroxylated bile acids have been proposed as putative ligands inducing transcriptional activity of LXR*a* (Song et al., 2000). Some ligands naturally present in the serum may also have an antagonistic effect on LXR as 7-ketocholesterol (Song et al., 2001).

Many pharmaceutical companies have screened potential LXR ligands. Among them T0901317 (Schultz et al., 2000) and GW3965 (Collins et al., 2002), two nonsteroidal synthetic LXR agonists, are commonly used in experimental studies. T0901317, in contrast with GW3965, is not completely selective for LXR (Viennois et al., 2011).

3.3 LXR expression patterns

LXR*α* was initially described as being highly expressed in a restricted subset of tissues known to play an important role in lipid metabolism such as liver, small intestine, kidney, spleen and adipose tissue whereas LXR*β* was found to be ubiquitously expressed (Viennois et al., 2011).

In the human placenta, both LXRα and LXRβ have been identified as early as the 6th week of gestation and can also be detected during gestation (Marceau et al., 2005). Indeed, mRNA expression is lowest in the first and second trimester of pregnancy (25 and 24% of term for LXR*a*, 33 and 16% for LXRβ, respectively). Expression levels in preterm and term placentae are similar to each other, but significantly higher than in the first two trimesters of gestation. The obligate heterodimeric partner of the LXRs, RXR, was found to be constitutively expressed throughout gestation (Plösch et al., 2010). Furthermore, both LXRs have been demonstrated to be expressed in choriocarcinoma trophoblast cell lines, e.g., JAR and BeWo (Weedon-Fekjaer et al., 2005).

3.4 Implications of LXRs in placenta and fetal membranes

3.4.1 Placental and amniotic presence of LXRs ligands

Placenta is an organ in which oxysterols are detected at a high concentration range (Schroepfer, 2000). Moreover, oxysterols such as 25-hydroxycholesterol (25-OHC) and 7-ketocholesterol (7-ketoC) circulate at low concentrations in normal conditions, but increase in maternal plasma as pregnancy advances (Aye et al., 2011). At low concentrations (2.5 μM) the oxysterol 22 (R)-OHC was shown to prevent first trimester extravillous cytotrophoblast invasion through the liver X receptor (LXR) which recognizes oxysterols as endogenous ligands (Pavan et al., 2004; Fournier et al., 2008b). Furthermore, the 7-ketocholesterol inhibit extravillous cytotrophoblast invasion. The role of LXR ligands in the placenta was confirmed using the LXR agonist T0901317, demonstrating the role of this nuclear receptor and its ligands in modulating the human trophoblast invasion (Pavan et al., 2004).

3.4.2 Fundamental implications of LXRs during early placentation

Little is known about the function of LXR during the placentation. A potential function of LXR in the placenta may be the regulation of cholesterol transport from the maternal to the fetal circulation. Indeed, cholesterol may be transported from the mother to the fetus to supplement the fetal cholesterol pool (Bełtowski & Semczuk, 2010). Conceptus implantation involves invasion of the uterine epithelium and the underlying stroma by extraembryonic trophoblast cells that undergo a complex process of proliferation, migration and differentiation. A specific feature of human placentation is the high degree of trophoblast invasion, greater than in other mammals. T0901317 has been shown to inhibit the invasiveness of cultured cytotrophoblast cells *in vitro* (Pavan et al., 2004). In addition, LXR mediates the inhibitory effect of oxidized LDL on trophoblast invasiveness.

3.4.3 Roles of LXRs in the uptake and transport of trophoblastic lipids

Compared with the liver, placenta secretes 50-200 times more fatty acid (Coleman & Haynes, 1987), indicating the importance of fatty acid as a mode of delivery of lipids to the fetus (Duttaroy, 2000). Noted that a new target gene, the long –chain acyl-coA synthetase 3 (ACSL3) was recently identified to illustrate the role of LXR as a regulator in fatty acid metabolism (Weedson-Fekjaer et al., 2010a). LXR has been demonstrated to be expressed in the placenta and in trophoblast-like cell lines, e.g., JAR and BeWo (Peet et al., 1998; Weedon-Fekjaer, 2005; Pavan et al., 2004). The increased fatty acid secretion by BeWo cells mediated by LXRs indicates its importance in placental lipid transport. Moreover, LXR activation in

trophoblasts would lead to increased expression of its target genes, e.g., ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1). Based on the localization of the ABCG1 and ABCA1 proteins to the basolateral (fetal) side of the trophoblast, one could assume that LXR activation would increase cholesterol flux from the maternal to the fetal circulation. Depending on the lipidation status of acceptor particles in the fetal circulation, both ABCG1- or ABCA1-dependent pathways seem to be possible, or even a combination of both. Therefore, LXR activation may be considered as a stimulus for increased transport of maternal cholesterol via the placenta to the fetal circulation (Plösch et al.,2007). Added to the fact that ABCA1 and ABCG1 are present on the syncytiotropholast (the maternal facing placental membrane), these results identify the inducible placental cholesterol transport by LXR as a preventive mechanism of placental accumulation of cytotoxic oxysterols (Aye et al., 2010).

3.4.4 LXRs in trophoblast invasion

Human implantation involves invasion of the uterine wall by trophoblastic cells and remodeling of uterine arteries by extravillous cytotrophoblasts (Henry-Berger et al., 2008). Several lines of evidence support the involvement of the LXR pathway in trophoblast biology. Firstly, trophoblast invasion is accompanied by an increased degradation of extracellular matrix proteins by members of the matrix metalloproteinases (MMPs) family (Caniggia et al.,1997), and expression of matrix metalloprotease-9 (MMP9) is regulated in macrophages by a mechanism dependent on LXR activation (Castrillo et al., 2003); secondly, T0901317 and oxidized LDLs (oxLDL), rich in oxysterols, significantly reduce trophoblast invasion via a mechanism involving LXRβ (Pavan et al., 2004; Fournier et al., 2008; Bełtowski & Semczuk, 2010). Recently Aye et al have shown that oxysterols inhibit syncytialisation and differentiation of term placental trophoblasts by activating LXRs. Excessive oxysterol exposure during pregnancy as a result of increased oxidative stress may, therefore, compromise placental formation and regeneration via inhibition of syncytialisation, thereby contributing to placental pathologies (Aye et al., 2011).

3.4.5 LXRs in placental pathologies

The pregnancy disease preeclampsia, a multisystemic disorder affecting about 5-10% of pregnancies towards the end of the second trimester of gestation, is still one of the leading causes of pregnancy-related maternal and fetal morbidity and mortality (Sibai et al., 2005; Myatt, 2002). Among its complications, intrauterine growth restriction and premature birth are of clinical relevance. Maternal predisposing factors such as diabetes, hypertension and obesity contribute to the consequences of this condition. Strong evidence supports that preeclampsia is generated by shallow invasion of the extravillous trophoblast into the decidua and an incomplete remodeling of the maternal uterine spiral arteries (Myatt, 2002). LXRβ mediates the inhibitory effect of oxidized LDL on trophoblast invasiveness, thus LXR agonists might interfere with the implantation process (Fournier et al., 2008). Moreover, inefficient trophoblast invasion may lead to subsequent impairment of placental perfusion, which is a main pathogenetic factor in preeclampsia. Furthermore, LXR agonists reduce the synthesis and secretion of hCG from trophoblast cells, which is mandatory for maintaining pregnancy in the first trimester (Weedon-Fekjaer et al., 2005). An increase in LXR and ABCA1 transporter levels point to an important role of ligands such as the oxysterols, which

may be increased in preeclampsia (Plösch et al., 2010). A positive correlation between placental LXRβ mRNA expression and placental free fatty acids was found in preeclampsia (Weedon-Fekjaer et al., 2010b).

Recently, T0901317 has been shown to increase the expression of endoglin, part of the transforming growth factor-β receptor complex. Endoglin is highly expressed in syncytiotrophoblast and inhibits trophoblast invasion (Henry-Berger et al., 2008). The human endoglin gene promoter contains six putative LXRE sequences and at least one of them binds the LXR/RXR heterodimer to stimulate transcription in response to 22(R)-hydroxycholesterol, T0901317 or synthetic RXR agonists (Henry-Berger et al., 2008). Interestingly, circulating endoglin level is increased in preeclampsia and may contribute to endothelial dysfunction associated with this disorder (Legry et al., 2008). Apart from stimulating endoglin, LXR agonists may reduce trophoblast invasiveness by down-regulating MMP9, as has been demonstrated in macrophages (Castrillo et al., 2003). The demonstration that LXRα together with ABCA1 can be regulated by hypoxia is another argument of the LXR involvement in preeclampsia, where the oxygen tension is described as abnormal (Plösch et al., 2010).

4. Conclusion

Since the discovery of the PPARs, there has been a marked increase in available data on their involvement in mammalian development. Concerning the placenta, all PPARs, but particularly PPARγ, are essential for multiple physiological functions of the trophoblastic and amniotic parts, leading to major involvement of PPARs in the pathophysiology of gestational diseases. However, special care must be taken when this particular PPAR signalling cascade is involved, because part of the regulation may involve PPAR ligand signalling but may be transduced by independent nuclear receptor pathways. This last point introduces a new level of complexity in PPAR biology. It does not close preclusion of the eventual use of PPARs for therapeutic treatment during pregnancy, but future medical applications seem still to be a long way off. We can reasonably expect to see some obstetrical use of PPARs in diagnosis (detection of PPARs mutations in intrauterine growth retardation, predisposition of preeclampsia) and therapeutics (tocolysis or treatment of chorioamniotis).

About LXR, a few recent publications show its involvement in obstetric pathologies such as preeclampsia, where he would reduce the invasiveness of extravillous trophoblast. Besides, the potential therapeutic application of LXR agonists may include increasing uterine contractility, (especially in conditions expected to increase cholesterol content in uterine myocytes, such as obesity, hypercholesterolemia or gestational diabetes mellitus) and stimulation of transplacental cholesterol transport for the prenatal treatment of inborn errors of cholesterol synthesis.

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This book contains the total of 19 chapters, each of which is written by one or several experts in the corresponding field. The objective of this book is to provide a comprehensive and most updated overview of the human placenta, including current advances and future directions in the early detection, recognition, and management of placental abnormalities as well as the most common placental structure and functions, abnormalities, toxicology, infections, and pathologies. It also includes a highly controversial topic, therapeutic applications of the human placenta. A collection of articles presented by active investigators provides a clear update in the area of placental research for medical students, nurse practitioners, practicing clinicians, and biomedical researchers in the fields of obstetrics, pediatrics, family practice, genetics, and others who may be interested in human placentas.

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