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PPARs and the Placenta

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Abstract

The discovery of the peroxisome proliferator-activated receptors (PPARs) in 1990s provided new insights in understanding the mechanisms involved in the control of energy homeostasis and in cell differentiation, proliferation, apoptosis and the inflammatory process. The PPARs became thus an exciting therapeutic target for diabetes, metabolic syndrome, atherosclerosis, and cancer. Unexpectedly, genetic studies performed in mice established that PPARγ are essential for placental development. After a brief description of structural and functional features of PPARs, we will summarize in this review the most recent results concerning expression and the role of PPARs in placenta and of PPARγ in human trophoblastic cells in particular.

Keywords: PPAR; Placenta; Cytotrophoblast; Differentiation

1. The peroxisome proliferator-activated receptors

Peroxisome proliferators-activated receptors (PPARs; for review, see [1]) are transcription factors belonging to the large ligand-activated nuclear receptor superfamily including the retinoic acid receptors (RAR), the thyroid hormone receptors (TR), the liver X receptors (LXR), the vitamin D3 receptors (VDR), and the steroid receptors (SR) [2]. In 1990, PPARs were first identified as receptors for fibrates, a class of hypolipidemic drugs used in humans since the late 1960s [3]. The name ''PPAR'' was initially chosen because of their ability to induce the proliferation of peroxisomes in rodents [4], but since the initial cloning in the mouse by Issemann and Green of the first PPAR isotype called PPARα, and the discovery of two additional isotypes (PPARβ/δ and PPARγ) by Dreyer et al. in 1992 [5], numerous studies have revealed that PPARs exhibit distinct tissue distribution patterns and control the expression of a large array of genes involved in lipid metabolism but also in the control of a broad range of cellular responses. Thus, PPARα is mainly expressed in the liver where it represents a major regulator of lipid catabolism and transport whereas PPARγ is highly expressed in white and brown adipose tissue and is an important determinant of adipocyte differentiation, lipid storage and glucose homeostasis. PPARβ/δ is ubiquitously expressed throughout the body and is involved in numerous biological processes including cholesterol transport and wound healing. In addition to these specific functions, the three PPARs isotypes share common functional features such as anti-inflammatory action and their implication in normal cellular differentiation and carcinogenesis. PPARs thus represent critical sensors of environmental/dietary stimuli that are crucial in the regulation of mammalian metabolism.

1.1. Structure of PPARs (Fig. 1)

To date, three PPAR isotypes encoded by distinct single-copy genes have been identified: PPARα (NR1C1), PPARβ or δ (NR1C2) and PPARγ (NR1C3), which are located on chromosomes 15, 17 and 6 in mouse and on chromosomes 22, 6 and 3 in human, respectively [6–9]. The human and

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mouse PPARγ genes generate three transcripts by alternate splicing and promoter usage: PPARγ1, PPARγ2 and PPARγ3. The translation of human PPARγ1 and PPARγ3 lead to an identical protein [10], whereas PPARγ2 has 30 additional amino acids in the N-terminal region due to the translation of an additional exon [11]. The PPARγ1 and PPARγ2 are the isoforms mainly expressed whereas the presence and the significance of PPARγ3 remain unclear. A common polymorphism affecting codon 12 of the PPARγ2 isoform substituting a proline for an alanine (Pro12Ala) has been found in several different populations [12]. The general structure of PPARs genes revealed a conserved genomic organisation of six coding exons that probably derive from a common ancestor [10,11,13,14]. PPARs are proteins of 49–56 kDa that contain multiple structural and functional domains, which are common to most nuclear receptors [15,16]. As shown in Fig. 1, PPARs are constituted of four main domains coded by six exons. The N-terminal A/B domain is the least conserved among the nuclear receptors and contains a ligand-independent transactivation domain called activation function 1 (AF-1). This domain was shown to interact with cofactors and contain conserved Map-kinase phosphorylation serine sites. The highly conserved C domain contains the DNA binding domain (DBD) that fold into two zinc fingers. The DBD is responsible for the recognition of the core hexanucleotide motif AGGTCA. As PPAR binds DNA as a heterodimer with the 9-*cis* retinoic acid receptor (RXR), functional PPRE (PPAR response element) is constituted by two copies of the core motif organized as a direct repeat spaced by one nucleotide (DR-1) [17] and a 5′-extension A(A/T)CT. Thus, PPAR/RXR heterodimer recognize response elements (PPRE) exhibiting the following consensus sequence 5′-**A(A/T)CT** (A/G)GGNCA A AG(G/T) TCA-3′ (the two canonical core motifs are underlined). The DBD contains a carboxyl-terminal extension (CTE) of the zinc finger domain that recognize the 5′extension of the DR1 (bold) contributing to the specificity and polarity of PPAR DNA binding. Indeed, unlike other nuclear receptors that form heterodimers with RXR, PPAR is located in 5′ of RXR on the PPRE [18,19]. The DBD is also involved in receptor dimerization [18]. The D or hinge domain linking the DBD to the ligand binding domain (LBD) is highly conserved and might be involved in nuclear localisation [20]. Recently, the hinge domain has been described to interact with regulatory proteins [21] and to contain consensus PKC phosphorylation sites [22]. The C-terminal E/F domain or LBD contains a large hydrophobic pocket that can bind a broad range of lipophilic

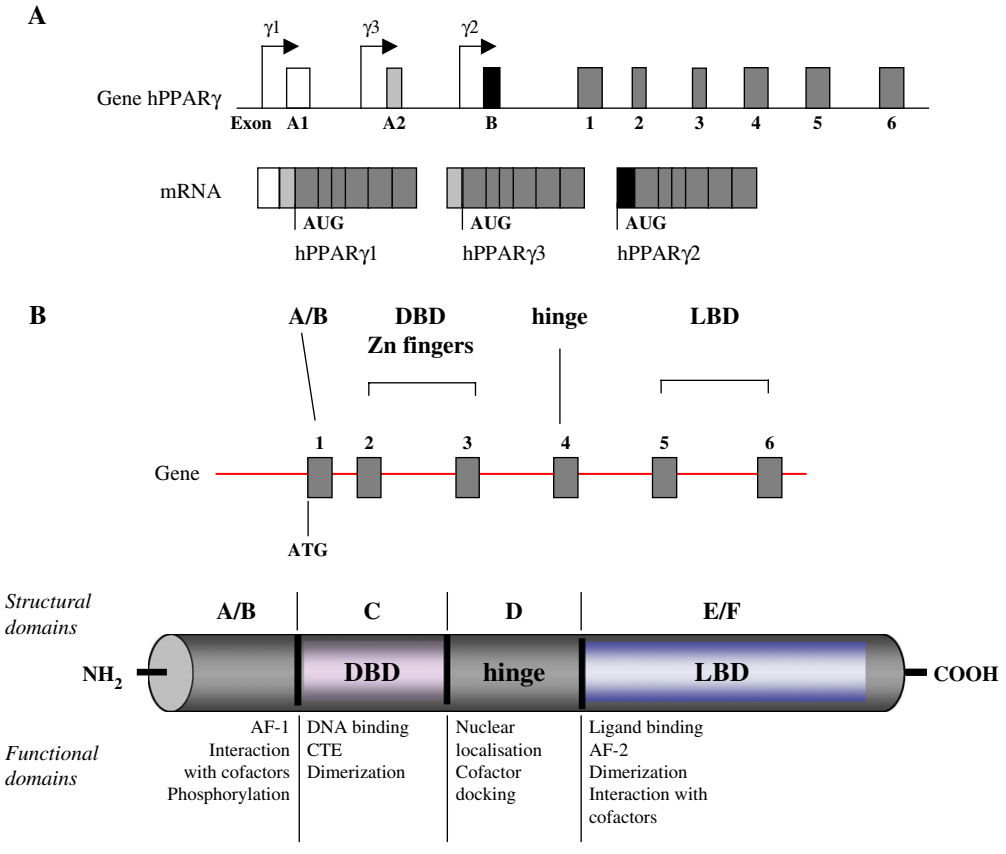

Fig. 1. Structure of PPARs. (A) Genomic organization of the human PPARγ gene. Alternative promoter usage and splicing results in three different transcripts (hPPARγ1, hPPARγ2, hPPARγ3) that encode two different proteins (hPPARγ1 and hPPARγ3 are translated into the same protein). (B) Structural and functional domains of PPARs. The dark boxes correspond to the six exons coding for the four domains of the protein: the A/B domain that contains the ligand-independent activation domain (AF-1); the DNA binding domain (DBD) constituted by two zinc fingers, the carboxyl-terminal extension (CTE) of the zinc finger domain contributes to the specificity and polarity of PPAR DNA binding; the D domain or hinge and the E/F region that binds the ligand and contains the ligand dependent activation domain (AF-2). Regions involved in interactions with cofactors, dimerization with RXR or containing phosphorylation sites or nuclear localisation signal are indicated.