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Biochimica et Biophysica Acta 1771 (2007) 999–1013
Biochimica et Biophysica Acta
BBA
www.elsevier.com/locate/bbalip

Review

PPARγ in human and mouse physiology

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Received 5 November 2006; received in revised form 14 March 2007; accepted 19 March 2007
Available online 27 March 2007

Abstract

The peroxisome proliferator activated receptor gamma (PPARγ) is a member in the nuclear receptor superfamily which mediates part of the regulatory effects of dietary fatty acids on gene expression. As PPARγ also coordinates adipocyte differentiation, it is an important component in storing the excess nutritional energy as fat. Our genes have evolved into maximizing energy storage, and PPARγ has a central role in the mismatch between our genes and our affluent western society which results in a broad range of metabolic disturbances, collectively known as the metabolic syndrome. A flurry of human and mouse studies has shed new light on the mechanisms how the commonly used insulin sensitizer drugs and PPARγ activators, thiazolidinediones, act, and which of their physiological effects are dependent of PPARγ. It is now evident that the full activation of PPARγ is less advantageous than targeted modulation of its activity. Furthermore, new roles for PPARγ signaling have been discovered in inflammation, bone morphogenesis, endothelial function, cancer, longevity, and atherosclerosis, to mention a few. Here we draw together and discuss these recent advances in the research into PPARγ biology.

Keywords: PPARγ; Mouse models; Human genetic variants; Longevity; Bone homeostasis; Metabolism

1. Introduction

Peroxisome proliferator-activated receptor-gamma (PPARγ, NR1C3) belongs to a nuclear receptor superfamily of transcription factors. It is mainly known to regulate adipocyte differentiation and fatty-acid uptake and storage (reviewed in [1–3]). The two distinct isoforms of PPARγ protein, PPARγ1 and PPARγ2, originate from one PPARγ gene through the use of separate promoters and 5′ exons (Fig. 1), and differ by the presence of an extra 28 (human)–30 (mouse) amino acids at the NH_2-terminal end of PPARγ2 [4–10]. This extension of the ligand-independent activation domain makes PPARγ2 a better transcriptional activator relative to PPARγ1 [11]. Not only the protein structure of PPARγ1 and 2 is different but both isoforms show also a distinct expression pattern. PPARγ2 expression is mainly limited to the adipose tissue whereas PPARγ1 is ubiquitously expressed [12,13]. The transcriptional activity of PPARγ is controlled by the promiscuous binding of small lipophilic ligands into the ligand-binding pocket. Although a natural compound exhibiting specific, high-affinity binding characteristics remains unidentified, endogenous polyunsaturated fatty acids and eicosanoids, derived from nutrition or metabolic pathways, have been recognized as ligands for PPARγ [14–16]. In addition, many synthetic compounds, most particularly the thiazolidinediones (TZDs), are potent PPARγ agonists (reviewed in [17,18]).

Human metabolism is evolutionarily equipped to cope with pre-agricultural cycles of feast and famine, and physical activity and rest. Because of the rapid emergence of the modern westernized life-style, exposing people to chronically elevated levels of natural PPARγ ligands and positive energy balance, our genetic makeup has become ill adapted to cope with our lifestyle [19–21]. The continual PPARγ activation promotes adipogenesis and fatty-acid storage, and eventually obesity and associated metabolic diseases such as hyperlipidemia, insulin resistance, type 2 diabetes mellitus (T2DM) and cardiovascular diseases including hypertension, which constitute a heavy social

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doi:10.1016/j.bbalip.2007.03.006

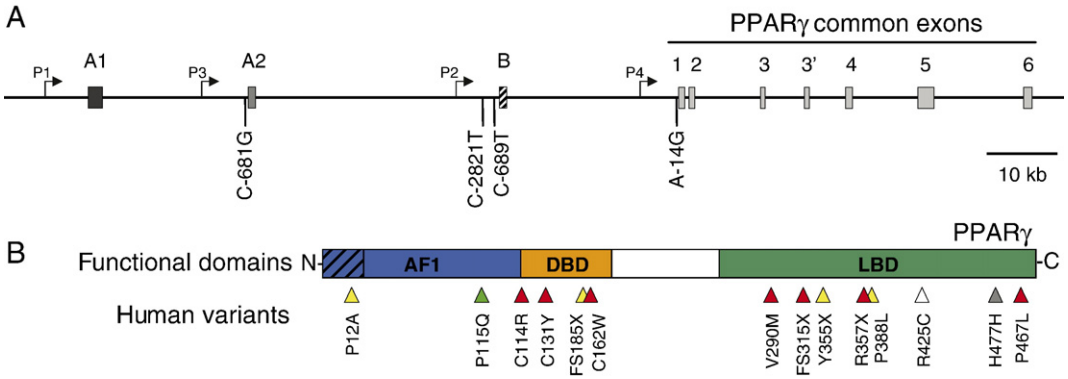

Fig. 1. Human PPARγ genetic variants. (A) Genomic structure of the human PPARγ gene (>150 kb) with thus far described promoter mutants below the structural scheme. Exons are presented as boxes with identification above. Exons A1 and A2 are non-coding, while B encodes for the N-terminal addition in PPARγ2 which is missing in PPARγ1. The exon sizes are exaggerated for clarity. Note the recently identified additional exon in the intron 3 which contains an in-frame stop codon and the use of which results in a truncated protein (Kim et al., Biochem. Biophys. Res. Commun. 347 (2006) 698–706). Promoters are indicated by angled arrows. Numbering for the promoter mutants is relative to the transcriptional initiation site for each promoter. (B) Functional structure of PPARγ protein with currently identified human PPARγ functional variants. Hatched section at the N-terminal end indicates the 28 amino acids specific for PPARγ2. AF1, ligand independent activation domain 1; DBD, DNA binding domain; LBD, ligand binding domain. PPARγ mutations are shown as arrowheads along the structural regions, color indicating the type of mutation as follows: green, gain of function; yellow, partial loss of function; red, loss of function, dominant-negative; grey, silent variant; white, unknown. Note that the amino acid numbering of the variants follows that of the originating publications, and thus some refer to PPARγ1, some PPARγ2. H477H is not likely to be a functional variant, but it is included here due to the fair number of papers associating it with various disease states.

and economic burden. Among the most potent current treatment strategies for T2DM are the TZDs which exert their antidiabetic effects by sensitizing the body to insulin's action. However, the clinical use of these full PPARγ agonists is limited by weight gain due to increased adiposity, fluid retention, and heart failure in up to 15% of patients [22–24]. In addition, despite their fairly wide use, the long-term adverse effects of TZDs are not very well known, and they may increase the risk for osteoporosis [25,26] and colon cancer [27,28].

In this review we summarize the studies that have shed new light on the role of PPARγ in energy homeostasis not only in the main metabolic tissues i.e. adipose tissue, liver and skeletal muscle, but also in other tissues. The reviewed studies also emphasize that insulin sensitization can be achieved without concomitant increase in fat deposition by modulating PPARγ activity. In addition to obesity, altered PPARγ activity, elicited by our westernized lifestyle, has potentially influenced bone homeostasis, longevity, cardiovascular and kidney function and cancer risk, as recent literature supports a significant role for PPARγ in these processes. Furthermore, animal models with altered PPARγ activity have elucidated the distinct roles of PPARγ in various tissues, as well as PPARγ-dependent and independent actions of TZDs therein. We can introduce here only a fraction of the existing information on this nuclear factor, and will thus mostly concentrate on the lessons learned from the study of various natural or engineered genetic variants of PPARγ that have altered PPARγ activity.

2. Human PPARγ genetic variants

The vital role of PPARγ in adipogenesis began to emerge more than a decade ago [12] and has remained undisputed since. Both of the processes central in adipogenesis, namely preadipocyte differentiation and fatty acid storage in mature adipocytes, are controlled by PPARγ, and particularly the PPARγ2 isoform (reviewed in [2,3,20,21]). Genetic association studies in humans underscore the role for PPARγ in adipogenesis as well as the complexity of PPARγ biology. One of the first links was the discovery that PPARγ locus on chromosome 3p25–p24 associates with obesity in Pima Indians [29]. To date, dozens of reports have revealed associations of genetic variation and population risk to T2DM or related conditions, as summarized in Table 1 for Pparγ. The most widely reproduced association is that with the PPARγ2 gene polymorphism Pro12Ala (Fig. 1B) [30,31] which has been suggested to induce a modest impairment of transcriptional activation due to decreased DNA-binding affinity [31,32]. The original reports describing a significantly reduced risk of T2DM in the normal-weight carriers of the Ala12 allele [30,31] have subsequently been confirmed by many independent studies, as reviewed in [2], and by recent meta-analyses [33–35]. For example, a meta-analysis compiling over 25,000 cases of diabetes unequivocally confirmed the association between the PPARγ Pro12 allele and T2DM, and suggested that patients who carry the Pro12 allele have a 1.27-fold higher risk for developing T2DM than Ala12 carriers [33]. This seemingly modest effect translates into a staggering 25% population-attributable risk because of the high frequency of the Pro12 allele (up to ~80–100%), especially in Japanese and European populations [33].

Genes do not work in a vacuum, but react to e.g. environmental stimuli. Clear demonstration of this, in the context of Pparγ, is the apparently paradoxical linkage of the Ala12 allele to *higher* body mass index (BMI) in obese (BMI ≥ 27) subjects [34]. Thus, co-existing obesity may be required for the Ala12 allele to cause further increase in obesity, whereas in lean subjects the effect is either lacking [34] or opposite [31,36]. Furthermore, the phenotypic effects of PPARγ Pro12Ala variant, also other than those on BMI and T2DM, have been shown to be modulated by the superimposition of environmental factors like obesity, physical activity, and the