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Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) and Neurodegenerative Disorders

Yu-Chang Chen · Jui-Sheng Wu · Hsin-Da Tsai · Chien-Yu Huang · Jin-Jer Chen · Grace Y. Sun · Teng-Nan Lin

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Abstract As the growth of the aging population continues to accelerate globally, increased prevalence of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, has generated substantial public concern. Unfortunately, despite of discoveries of common factors underlying these diseases, few drugs are available to effectively treat these diseases. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-activated transcriptional factor that belongs to the nuclear hormone receptor superfamily. PPAR-γ has been shown to influence the expression or activity of a large number of genes in a variety of signaling networks, including regulation of insulin sensitivity, glucose homeostasis, fatty acid oxidation, immune responses, redox balance, cardiovascular integrity, and cell fates. Recent epidemiological, preclinical animal, and clinical studies also show that PPAR-γ agonists can lower the incidence of a number of neurological disorders, despite of multiple etiological factors involved in the development of these disorders. In this manuscript, we review current knowledge on mechanisms underlying the beneficial effect of PPAR-γ in different neurodegenerative diseases, in particular, AD, PD, and stroke, and attempt to analyze common and overlapping features among these diseases. Our investigation unveiled information suggesting the ability for PPAR-γ to inhibit NF-κB-mediated inflammatory signaling at multiple sites, and conclude that PPAR-γ agonists represent a novel class of drugs for treating neuroinflammatory diseases.

Keywords Transcription factor · Stroke · Alzheimer's disease · Parkinson's disease · Inflammation

Y.-C. Chen · J.-S. Wu · H.-D. Tsai · C.-Y. Huang · J.-J. Chen · T.-N. Lin (✉)
Neuroscience Division, Institute of Biomedical Sciences,
Academia Sinica,
Rm 404,
Taipei 11529, Taiwan, Republic of China
e-mail: bmltn@ibms.sinica.edu.tw

G. Y. Sun
Department of Biochemistry, University of Missouri,
Columbia, MO, USA

Introduction

It is estimated that 40 million people in the USA are currently 65 years and older, and this number is projected to increase to 89 million (~20 % of total population) by 2050 [1]. The increase in aging population is associated with increasing prevalence of neurodegenerative diseases, characterized by the progressive dysfunction, deterioration, and eventual loss of neurons in the nervous system. Aging is a major risk factor for neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke.

The central nervous system (CNS) serves to transmit signals and coordinate actions in different parts of the body and to integrate information and coordinate body activities including movement, speech, swallowing, senses, breathing, learning, memory, and mood. According to the website of National Institute of Health in US, there are more than 600 neurological diseases, which can be categorized to heritable diseases (such as Huntington's disease and muscular dystrophy), developmental disorders (such as cerebral palsy), degenerative diseases of adult life (such as Parkinson's disease and Alzheimer's disease), metabolic diseases (such as Gaucher's disease), cerebrovascular diseases (such as stroke and vascular dementia), trauma (such as spinal cord and head injury), convulsive disorders (such as epilepsy), infectious diseases (such as AIDS dementia), and brain tumors.

The etiology of neurodegenerative diseases is diverse, and many exhibit a combination of both genetic and environmental factors [2]. The complex manifestations of different diseases make it difficult to suggest a unifying mechanism for disease initiation and progression. However, there are recognized common features suggesting common signaling cascades for these diseases. Current hypotheses for these neurodegenerative disorders include genetics, such as trinucleotide repeat disorders, genetic mutation, and selective vulnerabilities, aberrant protein structure, protein misfolding, protein clearing damage, mitochondria dysfunction, oxidative stress, programmed cell death, inflammation/immune imbalance, environmental toxin, infection, neurovascular damage and others ([3–6]; Neurodegeneration, Wikipedia; Table 1).

Peroxisome proliferator-activated receptors (PPARs or NR1Cs) are ligand-modulated transcriptional factors belonging to the nuclear hormone receptor superfamily. PPAR was originally cloned from liver peroxisomes, organelles that participate in fatty acid metabolism [7]. To date, three novel members have been cloned, namely, PPAR-α (NR1C1), PPAR-β/δ (NR1C2), and PPAR-γ (NR1C3 or glitazone receptor), which are encoded by three distinct genes located on human chromosomes 22, 6, and 3, respectively [8, 9]. These three PPAR isoforms share a high degree of structural similarity. Aside from mediating peroxisome proliferation, PPARs can also regulate other metabolic activities such as insulin sensitivity, glucose homeostasis, and fatty acid oxidation [10, 11]. Hereditary disorders of all PPAR isoforms have been described and generally lead to a loss of function and concomitant lipodystrophy, insulin resistance and/or acanthosis nigricans [12, 13]. Beyond these metabolic effects, PPAR activation is also involved in other physiological events such as blood pressure lowing, vascular protection, anti-inflammation, anti-oxidant, anti-apoptosis, cell proliferation, angiogenesis, differentiation, and anti-metastasis effects in different organs [14–24]. These pleiotropic effects overlap with many of the hypotheses underlying the pathogenesis of neurodegeneration (Table 1), and justify PPAR agonists as protective agents for neurological diseases.

Although all three isoforms of PPARs have been implicated in brain damage, their actions remain to be fully elucidated [25, 26]. PPAR-γ is the most extensively studied among these three isoforms [23]. PPAR-γ knockout is embryonically lethal [27]. During the past decade, many studies have demonstrated the neuroprotective effects of PPAR-γ agonists in a variety of preclinical models of neurological disorders. In this review article, our focus is mainly on the role of PPAR-γ in stroke, AD, and PD with attempts to analyze their interactions among various signaling pathways in the brain.

PPAR-γ Gene

Human PPAR-γ gene is mapped to chromosome 3 at position 3p25 while the mouse and rat genes are found in chromosome 6 and 4, respectively. The PPAR-γ gene consists of exons 1–6 in the open reading frame. Exons 2, 3, and 4 encode the DNA-binding domain, and exons 4, 5, and 6 encode the ligand-binding domain (LBD). Located in the C terminus of the LBD is the ligand-dependent activation domain, AF-2. This region is intimately involved in binding the receptors' coactivator. A ligand-independent activation function, AF-1, is found in close proximity to the N terminus of the receptor ([28]; NCBI).

The 5′terminal is the most variable and is the determinant of *PPAR-γ* transcript isoforms. Up-to-date, two highly

Table 1 Simplified overview of the current hypotheses for neurodegenerative disorders

Genetics	Trinucleotide repeat disorders: CAG repeat (polyQ) and non-polyQ
	Genetic mutations: PARK1, APP, Presenilin, SOD1, DJ1, TAR-DP, FUS, and ApoE4
	Selective vulnerabilities: AD—cholinergic neuron; PD—dopaminergic neuron; HD—GABAergic neuron; ALS—motor neuron; FTD—frontotemporal cortical neuron
Aberrant protein structure	Abeta, Tau, a-synuclein, HTT, ATXN, and TDP-43
Protein misfolding	Prion hypothesis
Protein clearing damage	Ubiquitin–proteasome and autophagy–lysosome systems
Mitochondrial dysfunction	DNA mutation, energy imbalance, free radical generation, and disease protein interaction
Oxidative stress	ROS and RNS
Programmed cell death	Apoptosis, autophagy, and aponecrosis
Inflammation/immune imbalance	Macrophage, microglial, cytokines, and chemokines
Environmental toxin	Herbicide, pesticide, and alcohol
Infection	Bacteria and virus
Neurovascular damage	Reduction of blood perfusion (brain hypoxia) or/and BBB dysfunction
Others	Ca^{2+} dysregulation; neurotransmitters malfunction; membrane permeability; trafficking and plasticity in axons and dendrites

conserved transcripts, *mPPAR-γ1* and *mPPAR-γ2*, have been identified in mouse [29]; three transcripts, *rPPAR-γ1a*, *1b*, and *2*, in rat [30, 31]; seven transcripts, *MPPAR-γ1~7*, in monkeys [32]; and six transcripts, *hPPAR-γ1~5* and *7*, in human [33]. Nevertheless, only four transcripts are listed in the NCBI data bank (Fig. 1). The reason for the different transcripts among species is not known, and their specific functions remain to be studied. Interestingly, Chen et al. [33] indicated that a PPAR-γ-specific ligand thiazolidinediones (TZD) could induce the expression of *PPAR-γ5* and *7* transcripts but inhibit the expression of *PPAR-γ1* and *2* transcripts in human. Ironically, TZD induces the expression of *PPAR-γ1* and *2* in rodent. *PPAR-γ2* is expressed mainly in adipose tissue and is the most studied isoform in mice. Obviously, differential regulation of *PPAR-γ* transcripts among species deserves further study.

These different transcripts encode for two major proteins: (1) a ~57.6 kD (505 amino acids, long form) protein named mPPAR-γ2 for *mPPAR-γ2* transcript in mouse; rPPAR-γ2 protein for *rPPAR-γ2* transcript in rat; and hPPAR-γ2 protein for *hPPAR-γ2* transcript in human; and (2) a ~54.5 kD (475/477 amino acids, short form) protein named mPPAR-γ1 for *mPPAR-γ1* transcript in mouse; rPPAR-γ1 protein for *rPPAR-γ1a* and *rPPAR-γ1b* transcripts in rat; and hPPAR-γ1 protein for *hPPAR-γ1*, *hPPAR-γ3*, and *hPPAR-γ4* transcripts in human (Figs. 1 and 2). There is one amino acid (E24D) difference between mPPAR-γ1 and rPPAR-γ1 (475 A.A.; 99.58 % homology), whereas two amino acids (S8P and E54D) difference between mPPAR-γ2 and rPPAR-γ2 (505 A.A.; 99.21 % homology). Furthermore, mouse PPAR-γ protein share higher homology with human PPAR-γ protein than rat PPAR-γ protein (Fig. 2). Again, the existence and physiological role for multiple protein isoforms is largely unknown.

PPAR-γ and Gene Transcription

PPAR-γ form heterodimers with the retinoid X receptor (RXR), which is activated by 9-cis retinoic acid. There is no known role for RXR within the PPAR/RXR complex; however, synthetic RXR agonists can also activate this complex, leading to anti-diabetic outcome [12]. The heterodimers then bind to specific DNA sequences called peroxisome proliferator response elements in the promoter of target genes. In the absence of ligand, heterodimers associate with co-repressor complexes which repress target genes. In the presence of ligands, PPAR/RXR binds to co-activator complexes and initiates transcription of target genes [10, 11].

A broad spectrum of PPAR-γ ligands has been identified and can be divided into three major groups [8, 34, 35]. (A) *Natural (endogenous) agonists* which can be further divided into four subgroups: (1) unsaturated fatty acids (such as DHA and linoleic Acid); (2) eicosanoids (such as 15d-PGJ_2 and PGA_1); (3) oxidized phospholipids (such as azPC and LPA); and (4) Nitroalkenes (such as LNO_2 and OA-NO_2). Among these compounds, the cyclopentenone prostaglandin 15-deoxy-$\Delta^{12,14}$ PGJ_2 (15d-PGJ_2) not only is the most potent ligand, but is also by far the most commonly used naturally occurring ligand for PPAR-γ [20, 36]. (B) *Synthetic agonists* which can be further divided into five subgroups: (1) TZDs (also called glitazones); (2) non-TZD agonists; (3) dual-α/γ agonists (also called glitazars); (4) pan-α/δ/γ agonists; and (5) selective PPAR-γ modulators (SPPAR-γM). Among these, TZDs were the first ligand discovered to bind and activate PPAR-γ in diabetic patients [37]. However, these compounds have adverse effects including weight gain, peripheral edema, hemodilution, increased cardiac load and increased risk of heart failure [38, 39]. (C) *Synthetic antagonists* which include Bisphenol A DiGlyceryl Ether, GW9662, LG100641, PD068235, and SR-202. Antagonists are important tools to decipher the signaling and functions of PPAR-γ. So far, no endogenous antagonist for PPAR-γ has been reported. Nonetheless, ligand specificity is an inherent problem for using agonists [40, 41], and one should keep in mind that not all the effects of PPAR-γ ligands are purely PPAR-γ dependent.

PPAR-γ Transcriptional Regulated Genes

As a transcriptional factor, PPAR-γ has been shown to influence the expression of many genes either for activation or inhibition. However, using the set of molecules in Ingenuity's Knowledge Base, only some of these genes have been clearly demonstrated to involve transcription regulation (Fig. 3). A majority of these genes are involved in transcriptional activation, indicating that PPAR-γ prefers positive than negative regulation of these genes. PPAR-γ exhibits multi-faceted and multi-dimensional properties in modulating a variety of genes, such as transcription factors, nuclear receptors, G-protein-coupled receptors, transmembrane receptors, ion channels, transporters, enzymes, peptidases, kinases, and cytokine/growth factors are all transcriptional regulated by PPAR-γ. These gene products are widely located in the nucleus, cytoplasm, plasma membrane, and extracellular space. PPAR-γ is known to play important roles in the regulation of fatty acid/glucose metabolism, inflammation/oxidative stress/apoptosis, and cancer. We further grouped the PPAR-γ transcriptional regulated genes into three categories, according to the above mentioned functions. Interestingly, 26 genes are involved in overlapping properties in all three functions, indicating that the PPAR-γ signaling is highly conserved and shared a number of common features in both physiological and pathological conditions (Fig. 4a). When 26 genes were further analyzed

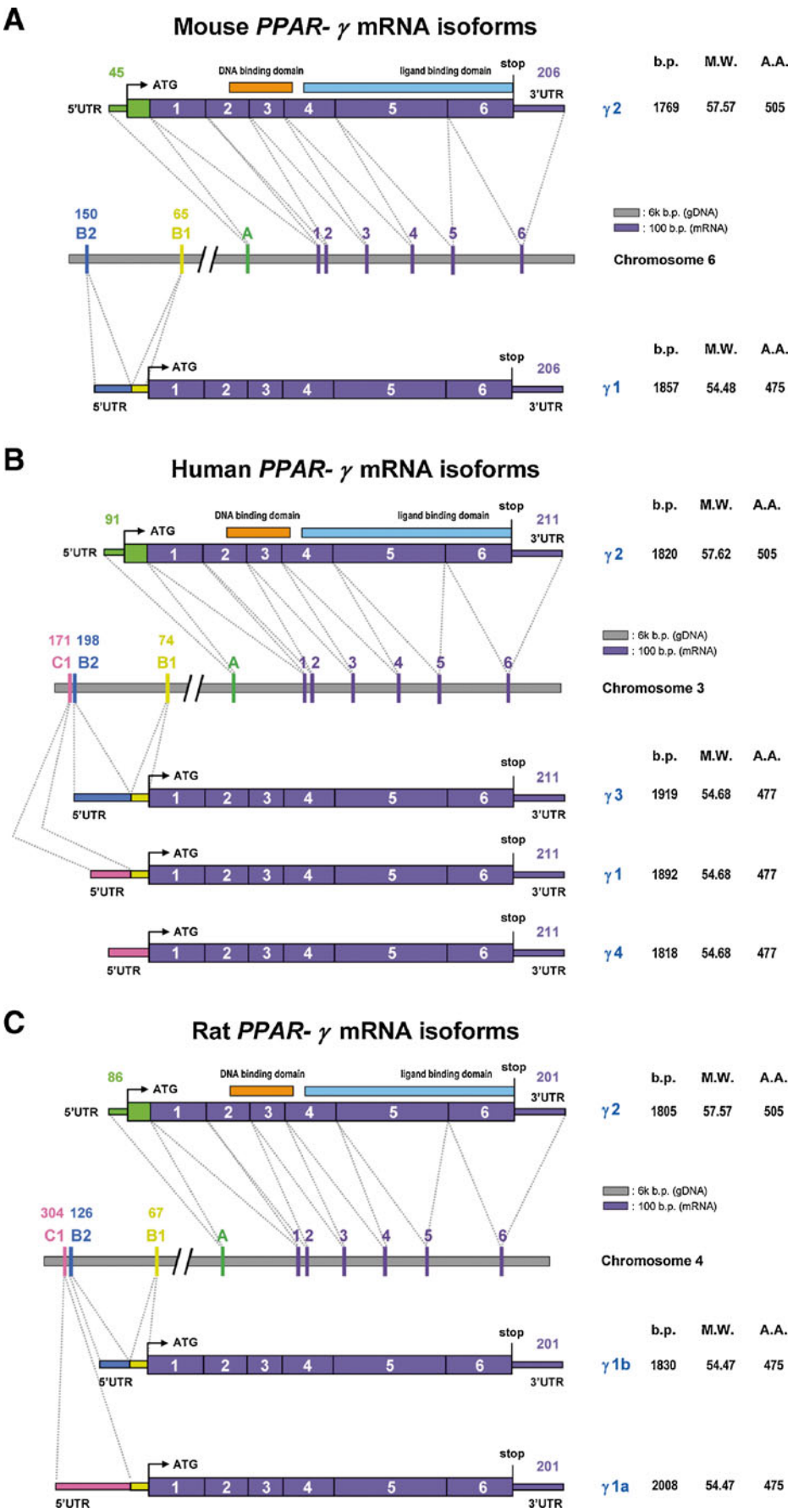

Fig. 1 cDNA structure of PPAR-γ isoforms of mouse (**a**), human (**b**), and rat (**c**) and the alignment of exons to its respective chromosome. Please note that the sequence identity of *rPPAR-γ1a*, *1b*, and *2* is equivalent to that of *rPPAR-γ3*, *2*, and *1*, respectively, in the NCBI data bank

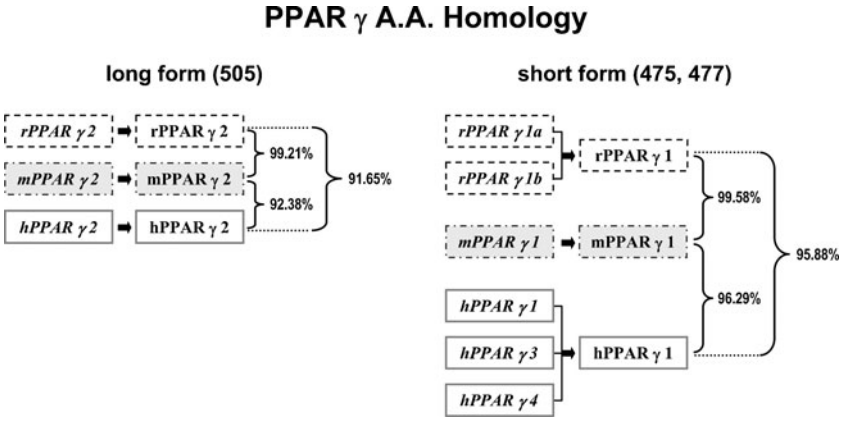

Fig. 2 Comparison of amino acids sequence homology of PPAR-γ isoforms among mouse, rat, and human

for possible interactions, a highly associated cluster of 12 genes was identified among them, in which, CCAAT/enhancer binding protein alpha (C/EBPα) plays a pivotal role. C/EBPs belong to a family of bZIP transcription factors, composed of six members named C/EBPα to C/EBP ζ. These factors promote the expression of genes through interaction with their promoter. These proteins are found in adipocytes, hematopoietic cells, neuronal cells, and cells in other organs. C/EBPs proteins are involved in different cellular responses such as those responsible for the control of cellular proliferation and differentiation, hematopoiesis, adipogenesis, energy metabolism, immunology, and many others. They are also intimately associated with tumorigenesis and viral diseases ([42]; Wikipedia). Intriguingly, besides PPAR-γ, C/EBPα can also enhance the transcriptional activity of the remaining 11 genes (Fig. 4b). It has been shown that C/EBPα and PPAR-γ are the two "master" adipogenic transcription factors required for both adipogenesis and normal adipocyte function. In this regard, C/EBPα co-localizes and functionally cooperates with PPAR-γ for adipocyte-specific gene expression [43, 44]. It is very likely that after transcriptional activation by PPAR-γ, C/EBPα, in return, teams up with PPAR-γ and synergistically enhances the transcription activity of PPAR-γ-regulated genes. This action would eventually lead to the attenuation of ROS production, apoptosis, and inflammation. A hypothetical cross talk among various signaling pathways is shown in Fig. 4b. It is important to know that a large number of genes that are also transcriptionally regulated by PPAR-γ cannot be specified as activation or inhibition due to conflicting results in the literature. This problem is probably due to the limitations in methodologies, inadequate sample numbers, cell type specificity, or variations in experimental conditions. For instance, 15d-PGJ_2 and TZDs at relatively low concentrations are anti-apoptotic, while at high concentrations are pro-apoptotic [20, 34, 45]. It is obvious that more efforts are needed to decipher these 11 genes in order to better understand the function of PPAR-γ.

Common Features of PPAR-γ Signaling in AD, PD, and Stroke

Besides direct transcription regulation, PPAR-γ also influences the expression of many other genes including transcription factors, co-activators or co-repressors; pancreatic and duodenal homeobox 1 (PDX1; or insulin promoter factor 1) is another good example besides C/EBPα. To better understand the involvement of PPAR-γ among different signal pathways in various neurodegenerative conditions, we analyzed genes whose expressions or activities are either directly or indirectly influenced by PPAR-γ according to the data bank of Ingenuity's Knowledge Base. With this data bank, 94 PPAR-γ regulated genes have link with AD research, 50 with stroke research, and 38 with PD research. Among them, 17 genes are identified in all three diseases conditions, some up-regulated (red), some down-regulated (green), and others unchanged (gray). Again, PPAR-γ signaling is highly conserved and shared a number of common features among neurological disorders (Fig. 5a). Upon further analysis of these 17 genes for possible interactions, it is surprising that all 17 genes are either directly or indirectly associated with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB was discovered by Sir David Baltimore and has been shown to play important roles in cellular responses to stimuli such as stress, cytokines, free radicals, and bacterial toxin or viral invasion, etc. NF-κB is a ubiquitous protein complex belonging to a unique class of transcription factors that are present in cells in an inactive state and do not require new protein synthesis to be activated. NF-κB is composed of homo- and heterodimers of five members of the Rel family including NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel (Rel). The p50/p65 heterodimer is the most abundant form of NF-κB. In unstimulated cells, the ankyrin repeat domains of inhibitor of κB (IκB) protein mask the nuclear localization signals (NLS) of NF-κB protein and keep them sequestered in an inactive state in the cytoplasm. Once activated, NF-κB translocates from the cytoplasm to the nucleus to activate gene

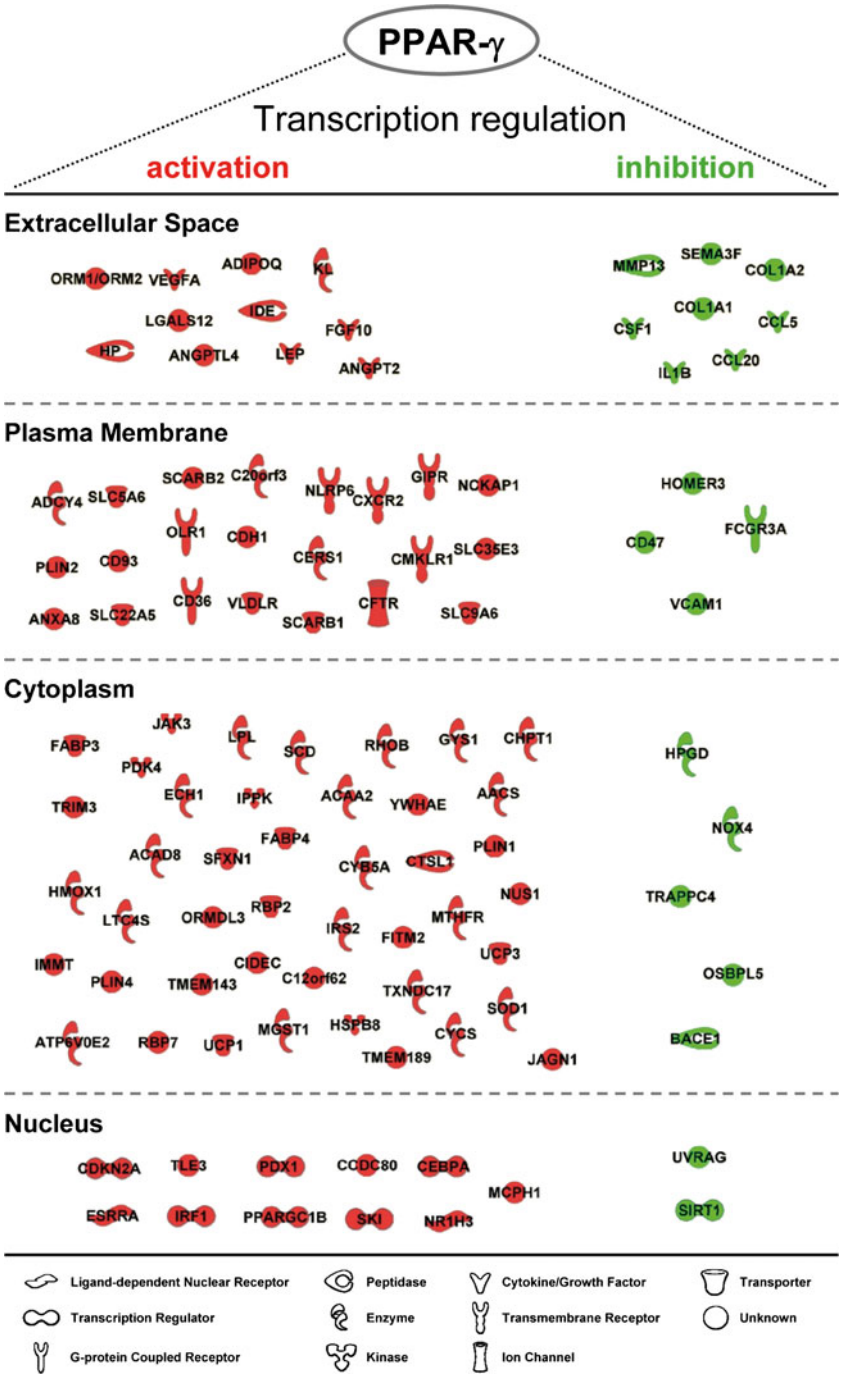

Fig. 3 A diagram indicating a wide range of genes with their transcriptional activities either activated (red) or inhibited (green) by PPAR-γ. The set of molecules used for analysis were obtained from information in Ingenuity's Knowledge Base. Red color: PPAR-γ increases gene expression; green color: PPAR-γ decreases gene expression; gray color: PPAR-γ regulates gene activity

transcription. There are two main NF-κB-activating pathways: (1) The canonical pathway, which is dependent on the activation of inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma (IKBKG, IKKγ, or NEMO), and subsequent phosphorylation and degradation of IκBα and nuclear translocation of mostly p65-containing heterodimers; (2) The noncanonical pathway, which is dependent on the activation of NF-κB inducing kinase (NIK) and IKKα in the formation and nuclear translocation of p52-RelB complexes [46–50]. NF-κB dysregulation has been linked to cancer, inflammation, and many other disease conditions.

A hypothetical NF-κB signaling cascade has been proposed from the above-mentioned genes and shown in Fig. 5b. Intriguingly, inflammation became the center of this deduced pathway. Inflammation is a physiological defense response, which serves to remove the pathogens or harmful stimuli and to initiate the healing processes. Without inflammation, wounds and infections would never heal; however, unregulated inflammation would cause tissue damage and endanger the survival of the organism. Despite the notion

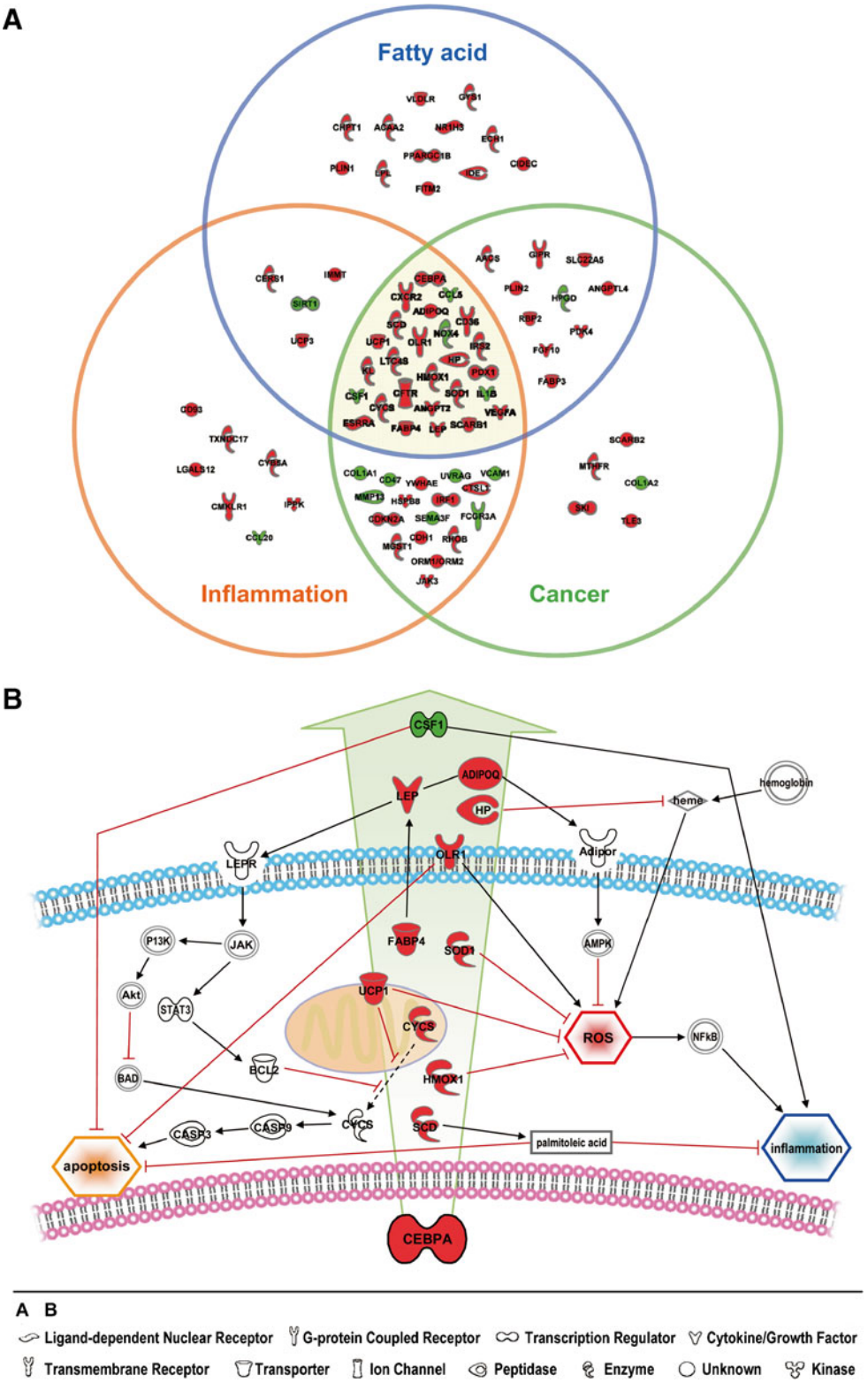

Fig. 4 PPAR-γ signaling shares a number of common features in both physiological and pathological conditions. **a** Genes listed in Fig. 3 are further grouped into three categories according to their functions, and their interactions are analyzed. **b** Eleven out of 26 genes in the overlapping area are also regulated by C/EBPα (or CEBPA). A hypothetical cross talk among various signaling pathways via PPAR-γ-C/EBPα axis is proposed. *Red color*: PPAR-γ increases gene expression; *green color*: PPAR-γ decreases gene expression; *gray color*: PPAR-γ regulates gene activity

that CNS is an immune-privileged organ, chronic inflammation can lead to progressive destruction of the tissue that results in a variety of immune and neurological diseases, such as stroke, AD, PD, Huntington disease, and multiple sclerosis [51]. PPAR-γ not only can attenuate the levels of pro-inflammatory mediators, such as IL-1, IL-6, MAP-1, CCL5, COX-2, iNOS, MMP-9, and TNF, but also can enhance the expression of anti-inflammatory mediators, such as IL-10, FAS, and methylenetetrahydrofolate reductase. On the other hand, PPAR-γ inhibits NF-κB activity by

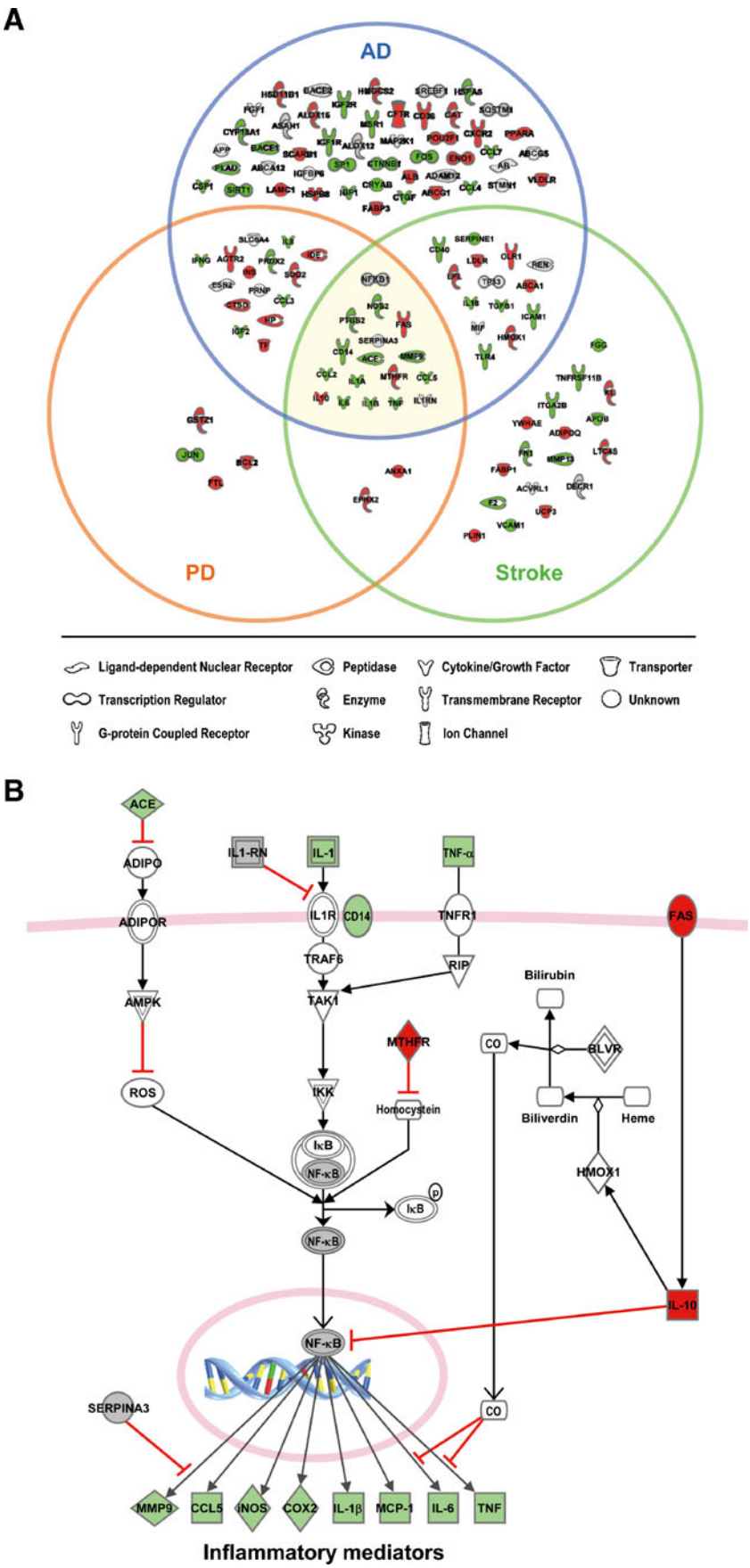

Fig. 5 PPAR-γ signaling shares a number of common features among AD, PD, and Stroke. **a** PPAR-γ regulates, direct and indirect, genes among disease conditions. **b** A hypothetical cross talk among various signaling pathways is proposed, and this includes entire 17 genes identified in all three diseases. *Red color*: PPAR-γ increases gene expression; *green color*: PPAR-γ decreases gene expression; *gray color*: PPAR-γ regulates gene activity

inhibiting NF-κB nuclear translocation and competing with NF-κB for co-activators, and activates SERPINA3 and IL1-RN (IL-1R antagonist). Together, PPAR-γ synergistically reduces the inflammatory signal cascade. Common anti-inflammation signaling pathways have also been observed in Huntington's disease and multiple sclerosis.

The deduced anti-inflammation pathway is in line with the current notion that the neuroprotective effects of PPAR-γ ligands are attributed to control of inflammation. The anti-inflammatory actions of PPAR-γ agonists have been extensively reviewed recently in ischemic stroke [8, 52–55], in AD [56–61], and in PD [62–66].

Summary

Neuroinflammation probably is the common pathological feature for neurodegenerative diseases. It is conceivable that the beneficial effects of PPAR-γ on a variety of neurodegenerative diseases can be attributed to its ability to regulate NF-κB signal networks. In this regards, PPAR-γ agonists represent a novel class of drugs for treating neuroinflammatory diseases. In fact, there are ongoing clinical trials using rosiglitazone to treat certain neurological disorders. However, one should keep in mind that rosiglitazone (Avandia; an FDA-approved thiazolidinedione for diabetes and agonist for PPAR-γ) has limitation to its use due to its association with adverse effects, namely hemodilution, anemia, weight gain, edema, and increased risk of heart failure. Epidemiological studies indicate that patients with a history using non-steroidal anti-inflammatory drugs (NSAID, COX1/2 inhibitor, and PPAR-γ agonist) have decreased risk for neurodegeneration, such as AD and PD, either by slowing down the progression or delaying the onset of neurodegenerative diseases. However, clinical trials with NSAIDs in AD patients have yielded conflicting results. It is very likely that these drugs may be beneficial only when used as prophylactic or at the beginning periods of disease. A collaborative effort is needed to ensure complete halting of the inflammatory signal cascade; solely inhibiting COX1/2 is probably not sufficient. In many instances, the BBB may be a problem in attenuating the efficacy of PPAR-γ agonists. In this regard, synthesis of more specific, potent, penetrable, and functional PPAR-γ agonists may lead to a better curative effect for neurodegenerative diseases and better understanding of the underlying mechanisms for neurodegeneration.

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The <*networks, functional analyses, pathways…etc.*> were generated through the use of IPA (Ingenuity Systems, www.ingenuity.com). The set of molecules are the user's dataset or molecules in Ingenuity's Knowledge Base (genes, endogenous chemicals, or both).

Conflict of Interest Authors declare no conflict of interest.

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