

Nuclear Receptors (PPARs)

Key References

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Overview

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. PPARs play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling. PPARs have been found to interact with a number of endogenous lipids and drugs for the treatment of human metabolic diseases.

There are three distinct PPAR subtypes which are the products of different genes and are commonly designated PPAR α [NR1C1], PPAR δ (also known as PPAR β and NUC1) [NR1C2] and PPAR γ [NR1C3]. Each receptor shows a differential pattern of tissue expression and is activated by structurally diverse compounds including endogenous long-chain fatty acids. PPARs have a highly conserved DNA binding domain (region C) and a diverse ligand-independent activation domain (region A/B) which can confer constitutive activity on the receptor. The C-terminal ligand-binding domain (regions E/F) is the site of ligand docking and has the most diversity between the pharmacologically distinct subtypes. X-ray crystallography of human PPAR isoforms has revealed important residues responsible for ligand binding, heterodimerisation and co-factor interactions.

PPAR α is expressed in tissues exhibiting high rates of β -oxidation such as liver, kidney, heart and muscle. In liver, PPAR α regulates lipid metabolism and in rodents, but not in man, PPAR α activation induces hepatomegaly and proliferation of liver peroxisomes. PPAR δ is ubiquitously expressed in tissues and has been implicated in energy

metabolism in both adipose and skeletal muscle. PPAR δ is abundant in many tissues during development especially in the adult rat digestive tract where a high rate of cell renewal and differentiation is required. PPAR γ is highly expressed in adipose tissue and is a key transcription factor involved in the terminal differentiation of white and brown adipose tissue. There is evidence that both PPAR α and PPAR γ could interfere with atherogenesis, in part by exerting an anti-inflammatory activity.

PPARs regulate gene expression by heterodimeric partnering with RXR (retinoid X receptors) and subsequent binding to specific response elements (PPREs) in the promoter regions of target genes. Structurally distinct PPREs are recognized by PPAR α , δ and γ . PPAR-RXR heterodimers can also be activated by ligand binding to either receptor partner independently.

A greater understanding of the mechanism of transcriptional regulation by nuclear receptors has led to the identification of multiple accessory proteins that bind to the nuclear receptors in a ligand-dependent manner. The nuclear receptor corepressor (N-CoR) or silencing mediator of retinoid and thyroid receptors (SMRT) proteins bind and mediate repression of transcription by the unliganded receptors. Coactivator proteins such as SRC1 and CBP/p300 are recruited by agonist bound receptors and promote initiation of transcription by remodelling the chromatin structure while coactivators such as the PPAR binding protein (PBP) and TRAP220 interact directly with the transcriptional machinery. The binding of ligand triggers a series of events which result in conformational changes involving recruitment of coactivators and dissociation of corepressors. The tissue specific expres-

sion of these cofactors may be responsible for the differential transcriptional regulation and responses observed in different cell types *in vivo*.

PPAR α agonists (fibrates) have shown therapeutic utility as lipid lowering agents whereas PPAR γ agonists such as the glitazones (thiazolidinediones) are marketed as antidiabetic agents. With the involvement of PPARs in many diverse metabolic pathways there is great clinical interest in the potential utility of PPAR ligands for the treatment of cancer, inflammation, psoriasis, atherosclerosis, dyslipidaemia, neurological disorders, obesity and diabetes.

Nuclear Receptors (PPARs)

CURRENTLY ACCEPTED NAME	PPAR α	PPAR δ	PPAR γ
OTHER NAMES	NR1C1	NR1C2, PPAR β , NUC1, FAAR	NR1C3
STRUCTURAL INFORMATION	468 aa (mouse and human)	440 aa (mouse), 441 aa (human), 506 aa (human γ 2)	475 aa (mouse), 475 aa (human γ 1)
TISSUE EXPRESSION	Liver, kidney, heart and muscle	Placenta, skeletal muscle but ubiquitously expressed	Adipose tissue, skeletal muscle, heart, lung, ovary
PHYSIOLOGICAL EFFECTS	Fatty acid synthesis, oxidation and ketogenesis	Fatty acid oxidation and cell cycle control	Adipocyte differentiation and glucose homeostasis
DISEASE RELEVANCE	Dyslipidaemia, atherosclerosis, inflammation	Metabolic syndrome, cancer	Diabetes, psoriasis, cancer, inflammation
SUBTYPE SELECTIVE AGONISTS (This data is compiled from multiple sources literature and from different human assays - binding assays and transactivation assays. Many compounds are known agonists at multiple PPARs. with different isoform selectivities) ^a	8(S) Hydroxyeicosa-tetraenoic acid (8(S)HETE) (H4019), LTB4 (L0517), Tetradecylthioacetic acid (TTA) (T1698), Wy-14643 (C7081), Clofibrate (C6643), Fenofibrate (F6020), GW9578, GW7647 (G0793), Merck Compound 12, KCL 1998001079, LY518674, LY6487, NNC 61-3058	Prostaglandin A ₂ (P4547), L-16504, ^b L-631033, GW501516, GW0742 (G3295)	15-Deoxy- $\Delta^{12,14}$ PGJ ₂ (D8440), hexadecyl azelaoyl phosphatidylcholine (azPC), Ciglitazone (C3974), Troglitazone (CS-045) (T2573), Pioglitazone (AD-4833) (P4120), Rosiglitazone (BRL-49653), LY171883 (L5408) L-805645, JTT-501 (malonic amide active metabolite), AD-5075, L-764406, CLX-0921, KRP-297, Farglitazar (GI262570), GW1929 (G5668), GW7845, GW0207, 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), PAT5A, glycyrin
NON SELECTIVE LIGANDS	L-796449, LY465608, Bezafibrate (B9273) ^c	L-796449, LY465608, Bezafibrate (B9273) ^c	L-796449, LY465608, Bezafibrate (B9273) ^c
PPAR α/γ SELECTIVE LIGANDS	SB-213068, SB-219994, LY1099, AZ242 (Tesaglitazar, Galida), BMS298585 (Muraglitazar), 9-Hydroxy-octadecadienoic acid (9-HODE), 13-Hydroxy-octadecadienoic acid, (13-HODE) (H9146), GW2331, NNC 61-0029 ((-) DRF-2725, Ragaglitazar), NNC 61-4424, NNC 61-4718, NNC 61-4705		SB-213068, SB-219994, LY1099, AZ242 (Tesaglitazar, Galida), BMS298585 (Muraglitazar), 9-Hydroxy-octadecadienoic acid (9-HODE), 13-Hydroxy-octadecadienoic acid (13-HODE), GW2331, NNC 61-0029 ((-) DRF 2725, Ragaglitazar), NNC 61-4424, NNC 61-4718, NNC 61-4705
PPAR α/Δ SELECTIVE LIGAND	GW2433	GW2433	Not known
PARTIAL AGONISTS AND ANTAGONISTS	GW6471 (G5045) (antagonist)	Sulindac (NSAID), ^d (S8139)	NC-2100 (partial PPAR γ agonist), Netoglitazone MCC-555 (partial PPAR γ agonist), FMOC-leucine (partial PPAR γ agonist) (47633, 408611), GW0072, ^e LG100641 (antagonist), PD068235 (antagonist), Bisphenol A diglycidyl ether (BADGE) (D3415), ^f L-764406, ^g GW9662 (M6191), ^g T0070907, ⁱ SR-202 (Mifobate) (S1320), ^j LG100754, ^k Diclofenac (D6899) ^l

FOOTNOTES

Nuclear Receptors (PPARs)

COACTIVATORS	PGC-1, CBP, CREB-binding protein/p300 interacting transactivator with ED-rich tail 2	SRC-2	PGC-1, PGC-2, SRC-1 (NCoA-1), PPAR binding protein (PBP) /DRIP205/TRAP220
COREPRESSORS	Not known	N-CoR, SMRT	SMRT/TRAC-2
INTERACTING PROTEINS ^h	RIP140, TRAP220, TRAP100	RIP140	TRAP100, DRIP
RADIOLIGANDS	[³ H]-GW 2331 [¹²⁵ I]-SB-236636	[³ H]-GW 2433 [³ H]-L-783483	[³ H]-BRL-49653 (rosiglitazone) [¹²⁵ I]-SB-236636 [³ H]-GW 2331 [³ H]-AD-5075

Abbreviations

CBP: CREB-binding protein

DRIP: Vitamin D receptor-interacting proteins

LTB₄: Leukotriene B-4

N-CoR: Nuclear receptor corepressor

NSAID: Non steroidal anti inflammatory

NCoA-1: Nuclear receptor coactivator

PGC: Peroxisome proliferator-activated receptor gamma coactivator

RIP: Retinoid X receptor interacting protein

SMRT: Silencing mediator of retinoid and thyroid receptors

SRC-1: Steroid receptor coactivator-1

TRAC: Thyroid hormone receptor-associated cofactor

TRAP: Thyroid receptor-associated proteins

FOOTNOTES

a Selectivity > 5 fold unless indicated otherwise.

b L-165041 has 2.6-fold selectivity for murine PPAR δ /PPAR γ but is 10-fold selective for human PPAR δ /PPAR γ and PPAR α .

c Human PPAR δ /PPAR α 2.5 fold selectivity and murine PPAR δ /PPAR γ selectivity 2-fold.

d Antagonist activity of compound under review.

e Antagonist but partial agonist in transactivation assays but inhibitor of adipocyte differentiation. Has reduced ability to recruit coactivators to the transcription complex.

f Antagonist inhibiting adipocyte differentiation but binds to PPAR γ in a binding assay.

g Irreversible PPAR γ ligand.

h Interaction only demonstrated *in vitro*.

i Increased NCoR recruitment.

j Decreased SRC-1 recruitment.

k RXR/PPAR γ agonist.

l Antagonist but can also act as a partial agonist.