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Overview of the structure-based non-genomic effects of the nuclear receptor RXRα

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Abstract

The nuclear receptor RXRα (retinoid X receptor-α) is a transcription factor that regulates the expression of multiple genes. Its non-genomic function is largely related to its structure, polymeric forms and modification. Previous research revealed that some non-genomic activity of RXRα occurs via formation of heterodimers with Nur77. RXRα–Nur77 heterodimers translocate from the nucleus to the mitochondria in response to certain apoptotic stimuli and this activity correlates with cell apoptosis. More recent studies revealed a significant role for truncated RXRα (tRXRα), which interacts with the p85α subunit of the PI3K/AKT signaling pathway, leading to enhanced activation of AKT and promoting cell growth in vitro and in animals. We recently reported on a series of NSAID sulindac analogs that can bind to tRXRα through a unique binding mechanism. We also identified one analog, K-80003, which can inhibit cancer cell growth by inducing tRXRα to form a tetramer, thus disrupting p85α–tRXRα interaction. This review analyzes the non-genomic effects of RXRα in normal and tumor cells, and discusses the functional differences based on RXRα protein structure (structure source: the RCSB Protein Data Bank).

Keywords: Nuclear receptor, RXRα, Non-genomic action, Modification, Structure, RCSB protein data Bank

Introduction

Nuclear receptors (NRs) are a group of transcription factors that are widely distributed in the body and can be expressed in the cytoplasm or nucleus. There are more than 200 known NR proteins and they are involved in a range of biological processes, including proliferation, differentiation, apoptosis, metabolism, migration, inflammation and immune responses [1, 2]. Disorders in the expression of NRs or their regulated genes can lead to conditions such as cardiovascular disease, diabetes, obesity, reproductive system diseases, inflammation, cancer and Alzheimer's disease [3–6].

RXRα (retinoid X receptor α; NR2B1), RXRβ (retinoid X receptor β; NR2B2) and RXRγ (retinoid X receptor γ; NR2B3) form a subgroup (the RXRs) belonging to the nonsteroidal receptor family of the NR superfamily [3]. The RXRs interact with ligands and co-regulators to regulate the coordinated expression of genes and thus play an important role in cell growth, development, homeostasis and many other physiological processes in the body [7–9].

RXRα, like the vast majority of NRs, consists of three distinct domains: an N-terminal A/B region that contains the ligand-independent activation domain AF1 (activation function-1); a DNA-binding domain (DBD); and a C-terminal ligand-binding domain (LBD) that contains the ligand-dependent activation domain AF2 (activation function-2). The LBD of RXRα also contains a canonical ligand-binding pocket (LBP), a co-regulator-binding surface groove and a dimerization surface [10–12].

RXRα regulates target gene transcription as a homodimer or heterodimer. RXRα homodimerizes with itself or heterodimerizes with many other nuclear receptors including peroxisome proliferator-activated receptor (PPAR), retinoic acid receptor (RAR), vitamin D receptor (VDR), thyroid hormone receptor (TR), liver X receptor (LXR), farnesoid X receptor (FXR), pregnane X receptor (PXR), chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII) and nerve growth factor-induced gene B (Nur77, NGFI-B) [9, 13–16].

9-*cis*-RA was the first identified endogenous ligand of RXRα. Many other small molecules have been identified that bind to RXRα and modulate its activities [17–19]. RXRα and its partners act as ligand-dependent transcription factors through binding to specific DNA-response elements of the target genes [20, 21]. After ligand binding, a conformational change in RXRα triggers a cascade of events, such as co-activator or co-regulator recruitment, leading to positive or negative transcription activities and subsequent exertion of different biological functions [22].

Accumulating evidence indicates that RXRα also has extranuclear non-genomic functions aside from its genomic function in DNA binding and transactivation [23–26]. RXRα migration from the nucleus to the cytoplasm is correlated to cell survival, differentiation, inflammation and apoptosis. The non-genomic actions of RXRα are predominantly due to its cleavage, modification and polymeric forms.

In this review, we will briefly introduce the functions of RXRα in some biological processes, discuss its modulation and non-genomic action based on recent research, and summarize the RXRα structures from the RCSB Protein Data Bank [27–29].

RXRα functions in various biological processes

The results of numerous experiments and biological analyses demonstrated that RXRα participates in a range of physiological processes. Altered expression of RXRα is involved in the development of many diseases. Genetic approaches in animals have shown that RXRα knockout is lethal at the embryonic stage [30, 31]. Active RXRα is required for ocular morphogenesis and the late steps in trophoblast differentiation [30, 31]. A reduction of RXRα expression in different tissues, such as the skin [32], adipose tissue [33], prostate tissue [34] and hepatocytes [35], may lead to various phenotypic changes, indicating that RXRα plays an irreplaceable role in these tissues.

Homodimerization of RXRα with itself or heterodimerization of RXRα with other nuclear receptors also affect its biological function. The phenotypes observed in most RXRα-knockout mice may be related to alterations in pathways regulated by its heterodimerization partners. RXRs heterodimerization with RARs is instrumental to retinoic acid signaling during embryonic development. Research has shown that binding of RXRα to PML–RARα is essential in the development of acute promyelocytic leukemia in transgenic mice, further illustrating the carcinogenicity of RXRα when it functions inappropriately [36]. RXRα–LXR heterodimers participate in AP1 signaling in

keratinocytes [37]. Recent findings indicate that an N-terminally truncated form of RXRα (tRXRα) produced in cancer cells resides in the cytoplasm, where it promotes the growth of tumor cells [38–43]. Proteolytic cleavage of RXRα, which could reduce RXRα expression or enhance truncated RXRα expression in tumor cells, is also correlated with the development of certain malignancies [38, 39]. Different subcellular localization or nucleus-to-cytoplasm shuttle of RXRα may also affect the development of cancer and certain diseases. In addition, changes in RXRα function through phosphorylation, acetylation, ubiquitination and SUMOylation are associated with the development of human diseases.

Modifications of RXRα

Limited proteolytic cleavage of RXRα protein has been found in many tumor cells [38–56]. Matsushima-Nishiwaki et al. found that RXRα was cleaved into tRXRα by m-calpain in HuH7 hepatocellular carcinoma (HCC) cells [38, 39]. Nomura et al. showed that in human placental choriocarcinoma JEG-3 cells, RXRα was cleaved into a 44-kDa tRXRα by the lysosomal enzyme cathepsin L-type protease at the RXRα N-terminal A/B region [40]. A 47-kDa tRXRα and 44-kDa tRXRα were detected in prostate cancer cell lines [41]. Recent studies showed that tRXRα is produced in many kinds of cancer cells and is detected in tumor tissues but not in normal tissues or tissues surrounding tumors in the same cancer patients [42–44]. Zhou et al. found that there is an N-terminal deletion of RXRα that lacks 80 amino acids. This tRXRα (RXRα-Δ80) can interact with the p85α subunit of the PI3K/AKT survival pathway and promote cancer cell proliferation in the majority of cancer cells [42]. In our study, tRXRα was detected in the cytoplasm while RXRα was detected in the nucleus [43]. We also found extensive intramolecular interaction between the N terminus and the C terminus (N/C) of full-length RXRα but not that of RXRα-Δ80, which explains why tRXRα can interact with p85α while full-length RXRα cannot [43]. The results of our study suggested that amino acids from 60 to 80 are critical for the RXRα N/C interaction. The N/C intramolecular interaction involves the N-terminal A/B domain and the C-terminal AF2/H12 [43]. Gao et al. identified a truncated RXRα that lacks 90 N-terminal amino acids and can activate AKT when overexpressed in cancer cells. They also investigated the role of calpain II in producing this kind of tRXRα [44]. Moreover, glycogen synthase kinase 3 beta (GSK-3β) can negatively regulate tRXRα production by inhibiting calpainII expression [44].

The N-terminal A/B domains of RXRα contain many phosphorylation sites, including serine 61, serine 75, threonine 87. Apoptosis is induced when hyperphosphorylation happened at these sites [45]. Serine 260 of RXRα, a consensus phosphorylation site of mitogen-activated protein kinase, is closely linked to RXRα-retarded degradation and the promotion of cancer cell growth in human HCC-derived HuH7 cells [46]. In addition, the non-genomic actions of RXRα also involve the inhibition of c-Jun N-terminal kinase (JNK) activation/phosphorylation and subsequent c-Jun phosphorylation. RXRα undergoes rapid post-translational modifications, including JNK-mediated phosphorylation, which correlates with a reduction in RXRα function [47–51].

Kopf et al. showed that in F9 murine embryonal carcinoma cells and transfected COS-1 African green monkey kidney fibroblast cells, nuclear retinoid receptors such as

RARα1 (retinoic acid receptor α1), RARγ2 (retinoic acid receptor γ2), and RXRα1 (retinoid X receptor α1) are degraded in a retinoic acid-dependent manner through the ubiquitin-proteasome pathway [52]. Aguirre et al. reported that lipopolysaccharide, tumor necrosis factor α (TNFα) and interleukin-1β rapidly and substantially stimulate SUMOylation of RXRα in human hepatocellular carcinoma HuH-7 cells, indicating that SUMOylation of RXRα is involved in the inflammatory signaling pathways [53]. Another study showed that p300 can induce acetylation of RXRα at RXRα lysine 145 (K145) [54]. The orphan nuclear receptor Nur77 exerts a negative regulation on p300-induced RXRα acetylation [54–56].

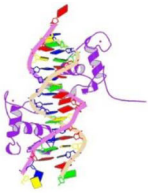
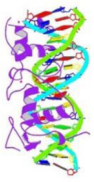
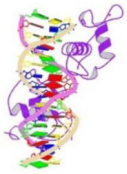
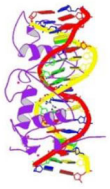
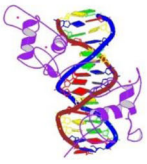
Different polymeric forms of RXRα

RXRα can form heterodimers with many nuclear receptors to assist in nucleus-to-cytoplasm transfer. Cao et al. found that in response to apoptotic stimuli, TR3 translocates from the nucleus to the mitochondria to interact with Bcl-2 and induce cytochrome c release, ultimately leading to cell apoptosis [57]. Mitochondrial targeting of TR3, but not its DNA binding and transactivation, is essential for its pro-apoptotic effect [55, 57, 58]. RXRα is required for the nuclear export and mitochondrial targeting of Nur77 through their unique heterodimerization. The effects of RXRα are attributed to a putative nuclear export sequence (NES) in its carboxyl-terminal region [57]. Interestingly, when treated with 9-*cis*-RA (the natural ligand of RXRα), RXRα is translocated with TR3 from the nucleus to the mitochondria, and apoptosis is induced [54, 55].

Zeng et al. revealed that an extract of *Hypericum sampsonii* had a remarkable effect on RXRα subcellular localization in various cancer cells [59]. Treatment of NCI-H460 human non-small cell lung cancer cells with *H. sampsonii* extract resulted in relocalization of RXRα from the nucleus to the cytoplasm, where it associated with mitochondria, leading to cytochrome c release and apoptosis. *H. sampsonii* extract effectively inhibits the growth of cells of various cancer cell lines, including H460 lung cancer, MGC-803 stomach cancer and SMMC7721 liver cancer. *H. sampsonii* fails to inhibit the growth of CV-1 African green monkey kidney fibroblast cells, which lack detectable RXRα, but transfection of RXRα into CV-1 cells restores the apoptotic response to *H. sampsonii*. This interesting phenomenon suggests that the growth-inhibiting effect of *H. sampsonii* extract depends on the RXRα levels. Furthermore, the apoptotic effect of *H. sampsonii* is significantly enhanced when RXRα is overexpressed in H460 cells. These results demonstrate that subcellular localization of RXRα is modulated by *H. sampsonii* which contains ingredient(s) that can induce apoptosis of cancer cells.

Another study showed that RXRα can assist ERΔDBD and ERΔHinge translocation from the nucleus to the cytoplasm. After treatment with E2 (steroid hormone 17β-estradiol), ERΔDBD returns to the nucleus while the ERΔHinge remains in the cytoplasm [60]. In studying the regulation of RARγ subcellular localization, Yan et al. observed that ectopically overexpressed RARγ is mainly cytoplasmic irrespective of serum concentration and cell density [61]. The cytoplasmic retention of RARγ is inhibited by the ligand all-trans-retinoic acid (ATRA). In addition, co-expression of RXRα results in nuclear localization of RARγ through their heterodimerization [62]. The nuclear receptor PPARγ (peroxisome proliferator-activated receptor γ) is a key regulator of glucose homeostasis and insulin sensitization. It must heterodimerize with its dimeric partner, RXR, to bind DNA and associated coactivators such as p160 family

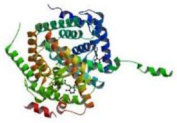
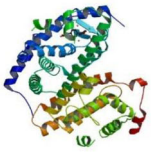
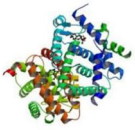
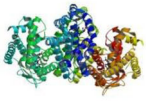
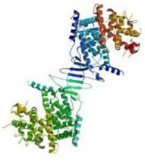
Table 1 The 3D structure of RXRα and DNA [84, 85]

PDB	Resolution	Released	Ref	Description	3D view
4CN3	2.35	2015-02-18	[84]	Crystal structure of the human RXR DBD bound to the human Gde1SpA response element	
4CN5	2.0	2015-02-18	[84]	Crystal structure of the human RXR DBD bound to the human Nr1d1 response element	
4CN7	2.34	2015-02-18	[84]	Crystal structure of the human RXR DBD bound to an idealized DR1 response element	
4CN2	2.069	2015-02-18	[84]	Crystal structure of the human RXR DBD bound to the human RAMP2 response element	
1BY4	2.1	2000-01-12	[85]	Structure and mechanism of the homodimeric assembly of the RXR on DNA	

members or PGC-1α [63]. Xu and Zeng found that the compound Z-10, a nitro-ligand of RXRα [64, 65], induces PML-RARα cleavage and APL cell apoptosis by disrupting PML–RARα–RXRα complexes in a cAMP-independent manner. RXRα is vital for the stability of both PML–RARα and RARα, likely through direct interactions. The binding of compound Z-10 to RXRα dramatically inhibits the interaction of RXRα with PML–RARα but not that with RARα, leading to Z-10's selective induction of PML–RARα but not RARα degradation. 1α, 25(OH)2D3 binds to the vitamin D receptor, which belongs to the NR family. This forms a complex with RXR to regulate gene expression. An interaction between RXR and VDR polymorphisms has been demonstrated, indicating that they have an impact on the risk of ovarian cancer [66, 67].

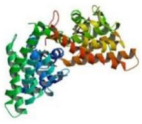
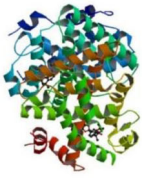
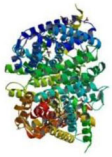
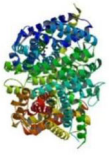
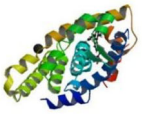
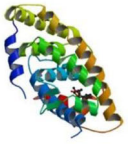
Besides heterodimers and its homodimer, RXRα can also form a tetramer. Zhang et al. identified danthron, which is extracted from the traditional Chinese medicine rhubarb, as a specific RXRα antagonist [68]. Danthron can bind to the tetrameric RXRα LBD in a specific stoichiometric ratio, and such binding can influence co-repressor

Table 2 The 3D structure of RXRα with other nuclear receptors [86–90]

PDB	Resolution	Released	Ref	Description	3D view
3A9E	2.75	2010-10-06	[86]	Crystal structure of a mixed agonist-bound RARα and antagonist-bound RXRα heterodimer LBDs	
4ZO1	3.221	2015-09-02	[87]	Crystal structure of the T3-bound TRβ LBD in complex with RXRα	
1DKF	2.5	2000-04-19	[88]	Crystal structure of a heterodimeric complex of RAR and RXR LBDs	
3FC6	2.063	2009-02-10	[89]	hRXRα and mLXRα with an indole pharmacophore, SB786875	
4J5W	2.8	2013-08-21	[90]	Crystal structure of the apo-PXR/RXRα LBD heterotetramer complex	
4J5X	2.8	2013-08-21	[90]	Crystal structure of the SR12813-bound PXR/RXRα LBD heterotetramer complex	

SMRT affinity to the receptor. The determined crystal structure of danthron-soaked RXRα LBD suggests a new mechanism for danthron antagonism to tetrameric RXRα [68]. We solved the crystal structures to reveal that the non-steroidal anti-inflammatory drug (NSAID) sulindac analog K-8008 can bind to the RXRα LBD tetramer through a novel hydrophobic region that is located on the surface of the monomer and near the dimer–dimer interface in the tetramer. Unlike the binding of other published ligands, the binding of K-8008 does not change the shape of the apo RXRα LBP, i.e., K-8008 binding may help to stabilize the RXRα LBD tetramer [69]. We also reported on the crystal structure of RXRα LBD in complex with K-80003, which is also derived from sulindac, and characterized the role of K-80003-mediated tRXRα tetramerization in regulating its interaction with p85α and non-genomic activation of PI3K signaling. Our results revealed a previously unrecognized role for RXRα tetramers in modulating subcellular localization and non-genomic interaction with cytoplasmic signaling proteins. We also showed that

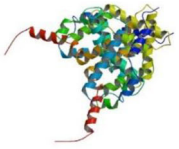
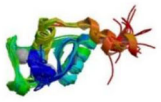
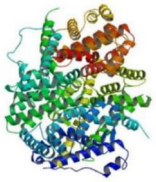
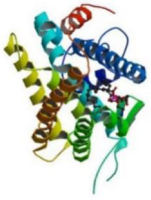
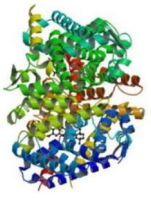
Table 3 The 3D structure of RXRα with compounds [43, 69, 91–94]

PDB	Resolution	Released	Ref	Description	3D view
1FBY	2.25	2000-07-28	[91]	Crystal structure of the human RXRα LBD bound to 9-*cis* retinoic acid	
1MV9	1.9	2002-10-16	[92]	Crystal Structure of the human RXRα LBD bound to the eicosanoid DHA (docosa hexaenoic acid) and a co-activator peptide	
1MZN	1.9	2002-10-23	[92]	Crystal structure at 1.9 angstroems resolution of the homodimer of human RXRα LBD bound to the synthetic agonist compound BMS 649 and a co-activator peptide	
5TBP	2.6	2017-08-09	[43]	Crystal structure of RXRα LBD complexed with synthetic modulator K8003	
4N5G	2.11	2014-05-14	[69]	Crystal structure of RXRα LBD complexed with a synthetic modulator K8012	
5MK4	2.0	2017-11-08	[93]	Crystal structure of the RXRα in complex with synthetic honokiol derivative 7 and a fragment of the TIF2 co-activator	
3OZJ	2.1	2011-02-02	[94]	Crystal structure of human RXPα complexed with bigelovin and co-activator SRC-1	

K-80003 inhibits tRXRα interaction with p85α by stabilizing a tetrameric form of tRXRα through a 'three-pronged' mechanism involving both canonical and non-canonical binding [43].

In conclusion, our results elucidated a previously unrecognized role for RXRα tetramers and demonstrated that conformational selection plays a critical role in the regulation of the non-genomic function of RXRα. We showed that the tetramerization of RXRα can be regulated by several mechanisms including ligand binding, intra domain interactions and non-genomic interactions with cytoplasmic signaling proteins [43].

Table 4 The 3D structure of RXRα [95–99]

PDB	Resolution	Released	Ref	Description	3D view
1LBD	2.7	1996-11-08	[95]	LBD of the human nuclear receptor RXRα	
1RXR	NULL	1998-11-11	[96]	High resolution solution structure of the RXR DBD, NMR, 20 structure	
1G1U	2.5	2001-04-25	[97]	The 2.5 angstrom resolution crystal structure of the RXRα LBD in tetramer in the absence of ligand	
1G2N	1.65	2001-04-21	[98]	Crystal structure of the ligand crystal structure of the ligand binding domain of the ultraspipacle protein USP, the ortholog of RXRs in insects	
5GYM	2.6	2017-11-01	[99]	Crystal structure of RXR-LBD complexed with fluorescent ligand at 2.60 angstroms resolution	

Different binding sites of RXRα for drug targeting

Canonical ligands bind to RXRα LBP to directly mediate RXRα transcriptional activity [3, 7, 10]. 9-*cis*-RA was the first compound identified as a natural RXRα ligand that binds to RXRα LDP and alters the ligand-binding pocket conformation. In addition, the synthetic RXRα agonist SR11237 1,3-dioxalane ring and the 9-*cis*-RA 19-methyl group occupy the same region of RXRα LBP [10]. The RXR-based drug Targretin (bexarotene), which is approved by the FDA for treating cutaneous T-cell lymphoma (CTCL patients), selectively binds to RXRs and does not have significant RAR binding and transactivation activity [7]. Several dietary fatty acids, including oleic acid, docosahexaenoic acid (DHA) and phytanic acid, bind RXRα and act as natural RXRα ligands [10, 11]. In addition to the RXRα ligands mentioned above, numerous natural products and synthetic compounds (retinoids) have been reported to bind to the RXRα ligand-binding pocket and to modulate its activities [17–19, 70–76].

Apart from the canonical ligand-binding site, many new alternate binding sites have been reported for nuclear receptors in recent years. Among these, the co-regulator-binding site is the most studied. Recently, by employing a docking-based virtual screening approach, Chen et al. identified a new RXRα antagonist, named compound 23, which can target the co-regulator-binding site of RXRα [77]. The compound does not bind to the ligand-binding pocket but to a hydrophobic groove on the surface of RXRα, a region where the binding sites of co-repressor and co-activator overlap [77]. This compound can also suppress AKT activation and thereby promote apoptosis of cancer cells in an RXRα-dependent manner by inhibiting tRXRα interaction with the p85α subunit of PI3K in vitro and in animals. Compound 23 is the first example of an RXRα modulator that acts via the co-regulator-binding site rather than binding to the classical LBP of RXRα.

We identified two new compounds, K-8008 and K-8012, which are NSAID sulindac analogs that can bind to the hydrophobic region of RXRα LBD near the entry and the edge of the cognate LBP [69]. The hydrophobic region does not overlap with the binding region of 9-*cis*-RA on RXRα. This new binding pattern explains why K-8008 and K-8012 compounds fail to compete with the binding of 9-*cis*-RA but can still inhibit cancer cell growth [69]. K-80003, another NSAID sulindac analog, promotes tetramerization of tRXRα but not RXRα. We solved the crystal structure of RXRα LBD in complex with K-80003 to a resolution of 2.6 Å. We found that the RXRα LBD–K-80003 complex adopts a tetrameric structure. These 'tetramer' interfaces comprise three sub-regions: parallel packing between symmetry-related H3 helices; 'end-to-end' packing at H11 that reduces their length by two helical turns (compared with the agonist--bound structure); and the invasion of each H12 helix into its apposing domain, where it binds to the co-regulator-binding groove, consisting of elements of H3 and H4 [43].

Summary of RXRα protein structures

The protein structure and formation of RXRα are very important for investigating its biological functions and developing RXRα-targeting drugs. Different structures and aggregation methods may lead to different forms of RXRα. The structure of RXRα is available from the RCSB Protein Data Bank (PDB; https://www.rcsb.org/) [29, 78–83].

Here, we organized and summarized the structures of the RXRα as reported in the PDB database, showing the 3D structures of RXRα complexed with DNA, the structures of RXRα with the other nuclear receptors, the structures of RXRα with various compounds and the structure of apo-RXRα (Tables 1, 2, 3, 4 and the Additional file 1: Table S1).

Conclusions and perspectives

RXRα is a nuclear receptor that regulates various biological effects such as cell growth, differentiation and apoptosis [3–9]. It plays a significant role in human physiology and pathology and can be regulated by endogenous and synthetic ligands and other small molecules. The continual discovery of new non-genomic actions of RXRα has greatly expanded our understanding of its cellular functions.

The effects of RXRα unrelated to its transcriptional activity have lately received increasing attention from researchers. Initially, it was noticed that upon certain stimuli,

RXRα translocates NR4A1 from the nucleus to mitochondria and triggers apoptosis [56–59]. Direct interaction of tRXRα with the PI3K/AKT signaling subunit p85α may cause cancer cell growth and appears to be a potential target for anti-cancer drug development [42, 43, 69–73]. RXRα is unique in that it can be cleaved, phosphorylated, ubiquited, SUMOylated and acetylated, and it can form not only homodimers and heterodimers but also homotetramers, suggesting that the equilibrium between these different states plays a role in regulating RXRα functions [6–12, 41, 49, 53, 55, 57, 62].

RXRα and tRXRα are intriguing targets for pharmacological intervention, so it is of great importance to discovery new strategies for targeting them. The development of compounds or inhibitors targeting tRXRα by binding to a novel binding site may lead to a departure from the traditional approach of targeting LBP and initiate a new paradigm for targeting the RXRα surface for more effective and specific therapeutics [7, 10, 11, 69, 77].

Our analysis based on data from the PDB shows that currently known RXRα structures can be used for structural and functional predictions for new drug development. Further studies on RXRα, including its involvement in signaling pathways, its various structures, and targeted drug development are still needed. Hybrid approaches combining a variety of biophysical, biochemical, biomathematical, bioinformatic and modeling techniques will be used increasingly to predict and determine the structure-based functions of the protein.

Critically, while RXRα functions as a transcription factor in the nucleus, it can also directly interact with other nuclear receptors or proteins in different cellular compartments to exert multiple biological functions. This makes it a fascinating and important subject for further research using the described methods.

Additional file

Additional file 1: Table S1. The 3D structure of RXRα with compounds. (DOCX 1855 kb)

Abbreviations

AF1: Activation function-1; AF2: Activation function-2; CTCL: Cutaneous T-cell lymphoma; DBD: DNA-binding domain; DHA: Docosahexaenoic acid; E2: Steroid hormone 17β-estradiol; GSK-3β: Glycogen synthase kinase 3 beta; JNK: c-Jun N-terminal kinase; LBD: Ligand binding domain; LBP: Ligand-binding pocket; NES: Nuclear export sequence; NRs: Nuclear receptors; NSAID: Nonsteroidal anti-inflammatory drug; PPARγ: Peroxisome proliferator-activated receptor γ; RA: Retinoic acid; RARα1: Retinoic acid receptor α1; RARγ2: Retinoic acid receptor γ2; RCSB PDB: RCSB Protein Data Bank; RXR: Retinoid X receptor; RXRα: Retinoid X receptor-α; RXRα1: Retinoid X receptor α1; RXRβ: Retinoid X receptor β; RXRγ: Retinoid X receptor γ; TNFα: Tumor necrosis factor α; tRXRα: Truncated RXRα

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Authors' contributions

LC, LW designed and supervised the project and wrote the manuscript. LZ and YZ participated in the discussion and read the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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