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A Compendium of Nuclear Receptors: The Superfamily of Ligand-Modulated Transcription Factors

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Abstract

The 'Nuclear Receptor Super-family' is a group of ligand-modulated transcription factors with 48 members identified in human genome. Members of this family of receptors are now established to be involved in regulation of a plethora of physiological processes in the paradigms of development, reproduction, metabolism and homeostasis. Also, in the myriads of patho-physiological processes, these receptors have consistently exhibited enormous potential as targets for the treatment of diseases such as cancers, osteoporosis, diabetes, obesity, coronary heart disease, asthma, hypertension, thyroid conditions and multiple other metabolic disorders. In recent times, it is estimated that about 15% of the clinical drugs, used in treatments of different ailments, target nuclear receptors. These receptors include steroid/thyroid hormone receptors and orphan/adopted receptors that function as intra-cellular transcription factors to regulate expression of several hundreds of genes in response to their cognate ligands. Interestingly, nuclear receptors are also being assigned a novel role in serving as 'epigenetic marks' for the retention and transmission of cellular 'transcriptional memory'. These receptors function primarily either as homodimers or heterodimers with Retinoid X Receptor (RXR) or sometimes as monomers. Being 'drug responsive' these receptors offer attractive targets for drug discovery since their activities can be favorably modulated by interacting ligands. However, many of the newly discovered members of this family of receptors remain incompletely understood, both in terms of physiological roles and activating ligands. In brief, nuclear receptors represent enormous potential for drug discovery and are continuously being examined to unravel the mysteries underlying their mechanisms of action. It has been well-over three decades since the cloning of steroid/nuclear receptors in the 1980s. Therefore, it's only appropriate to prepare a comprehensive review that provides a compendium of facts and events from receptor cloning and characterization to establishment of receptor domain structures, physiological functioning and consequences of receptor malfunctioning. This review is expected to serve as a refreshing compendium of nuclear receptors for both, the beginners, as well as experts working in the areas of nuclear receptor biology.

Keywords: Classification, Diseases, Diversity, Drug Targets, Epigenetics, Nuclear Receptors, Transcription Factors, Structure

LIST OF ABBREVIATIONS

AF-1: Activation Function-1
AF-2: Activation Function-2
ARC: Activator-Recruited Cofactor
BIOPIT: Biomolecular Imprints Offered to Progeny for Inheritance of Traits
COPD: Chronic Obstructive Pulmonary Disease
CYP: Cytochromes P450
DBD: DNA binding domain
D-Box: Distal (Dimerization) Box
DME: Drug metabolizing enzymes
DRIP: vitamin D receptor-interacting proteins
HAT: Histone Acetyltransferase
HDAC: Histone Deacetylase
HREs: Hormone Response Elements
HSP70: heat shock protein-70
HSP90: heat shock protein-90
LBD: Ligand Binding Domain
NCoR: Nuclear Receptor co-Repressor
NES: Nuclear Export Signal
NLS: Nuclear Localization Signal

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NMR: Nuclear magnetic resonance
NTD: N- Terminal Domain
P-Box: Proximal Box
SHR: Steroid Hormone Receptor
SMRT: Silencing Mediator of Retinoic acid and Thyroid hormone receptors
TRAP: Thyroid Receptor Associated Protein

1. Introduction

Nuclear Receptors (NRs) are evolutionary conserved proteins. The genes encoding these proteins are expressed in the animal kingdom (metazoans) but are not present in bacteria, protozoa, yeast or in plants. They are also reported to be present in animals that do not have any well-defined endocrine system[23,146]. They constitute a superfamily of specialized transcription factors of molecular masses ranging from 50-100 kilodaltons with similarity of sequence and structure. In general, they bind as homo- or hetero-dimers to the response elements having specific consensus sequences of DNA in the promoter regions of their target genes[4]. A total of 48 NRs are reported to be present in humans (Table 1), and these receptors control a broad array of genetic programs that in turn may be

Table 1. A compendium of updated information on 48 human Nuclear Receptors

S.N.	Name of Nuclear Receptor / Abbreviation/ NRNC Symbol	Amino acid residues	Chromosomal location / Accession number	Dimers (m, hd, RXR-h)	Ligand(s)	Major physiological Functions	Associated diseases	Target Genes	Initial full-length cloning
01.	Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 / DAX1 NR0B1	470	Chromosome X at position p21.3[173] NM_000475.4	-	Orphan	Lacks a DBD; inhibits the activity of other NRs by heterodimerization; involved in controlling the hypothalamic-pituitary axis, gonadal development, and sex determination	Reproductive, Endocrine	↓ P450C17 CYP19A1, MIS, STAR, AKR1B7 [SF-1]	Human:- Zanaria et al. 1994 [173]
02.	Small heterodimer Partner / SHP NR0B2	257	Chromosome l at position p36.1[93] – HQ692833.1	RXR-h	Orphan	Lacks a DBD; functions as a corepressor to inhibit the activity of NRs and other signaling pathways; involved in the regulation of cholesterol, lipid, and glucose metabolism.	Metabolic	↓ PLIN1 [ERRα]; ABCG1 [LXRα]; CYP7A1 [LRH-1]; INOS, PTGS2 [IL-1β]; AGT [HNF4α]	Human:- Seol et al. 1996[139]

03.	Thyroid hormone receptor-α / TRα NR1A1	410	Chromosome 17 at position q l1.2 to qiV[37,108,152] – M24748	RXR-h	Endogenous: Thyroxine (T4), Triiodothyronine (T3) Clinical: Levo-thyroxine, triiodothyroacetic acid (TRIAC) in resistance to thyroid hormone. Thyroid hormone	Regulation of oxygen consumption; protein, carbohydrate, lipid, and vitamin metabolism	Thyroid conditions, Cancer	↑ ADRB1, PCK2, GH1, UCP1; ↓ DIO2, EHHADH, PRL, EGFR	Human – Weinberger et al., 1986[165] Chicken Sap et al., 1986[137]
04.	Thyroid hormone receptor-β / TRβ NR1A2	456	Chromosome 3, position p25[39,164]- X04707	RXR-h					
05.	Retinoic acid receptor-α / RARα NR1B1	432	Chromosome17 position q21.1[18,38] – X06538	RXR-h	Endogenous: All-trans and 9-cis retinoic acid Clinical: Tretinoin for treating acne and acute promyelocytic leukemia	Pleiotropic control of embryonic patterning and organogenesis, cell proliferation, differentiation, apoptosis and homeostatic control	Neurological and psychiatric, cancer	↑ Numerous HOX genes, STRA6, HNF3A, CRABP2, ACADM, MECOM; ↓ CYP1A1, HOXB9	Human:– Petkovich et al., 1987; Giguere et al., 1987 Mice- Zelent et al., 1989[9,56,123]
06.	Retinoic acid receptor-β / RARβ NR1B2	448	Chromosome 3 position p24[102]- Y00291	RXR-h					Human:- Brand et al. 1988 Mouse:- Zelent et al., 1989
07.	Retinoic acid receptor- γ / RARγ NR1B3	454	Chromosome 12 position ql3[71,102]- M57707	RXR-h					Mouse:- Zelent et al., 1989[9] Human:- Krust et al., 1989[80]

08.	Peroxisome proliferator-activated receptor-α / PPARα NR1C1	468	Chromosome 22, slightly telomeric to 22ql2-ql3.1[59] – L02932	RXR-h	Endogenous: FAs and FA intermediates Clinical: Fibrates (e.g., fenofibrate) in hyperlipidemia Dietary:- FAs and PUFAs Xenobiotics: DEHP, DEHA	Regulating energy expenditure; modulating fatty acid oxidation systems (mitochondria), peroxisome β-oxidation, and microsomal ω-oxidation	Cardiovascular, metabolic, cancer, neurological	↑ ACBP, ACOX1, APOA1, CPT1A, CYP1A1, CYP4A1, CYP7A1, SLC27A1, LCAS, MLYCD, SCD, FADS2, RETN, MYC, CCND1, IGFBP1, UCP1, KRT23, IL6, TF, PEX11A	Mouse:- Issemann and Green 1990[71] Human:- Sher et al., 1993[141]
09.	Peroxisome proliferator-activated receptor-β/δ / PPAR-β/δ NR1C2	441	Chromosome6 position p21.1-p21.2[169]- L07592	RXR-h	Endogenous: FAs and FA intermediates Dietary: FAs and PUFAs	Regulating cell proliferation, differentiation, and migration in wound healing and inflammatory processes	Cardiovascular, metabolic, cancer, neurological	↑ ACSL3, CPT1A, RGS3, RGS4, RGS5, ISG20, CXCL7, CCL21, RETN, CPT1A	Human:- called NUCI by Schmidt et al., 1992[138] Mouse:- PPARδ by Kliewer et al. 1994[77]
10.	Peroxisome proliferator-activated receptor-γ / PPARγ NR1C3	478	Chromosome 3 position p25[58]- L40904	RXR-h	Endogenous: FAs and FA intermediates Dietary: FAs and PUFAs Clinical: Thiazolidinediones (e.g., rosiglitazone) in type II diabetes	Regulation of adipocytes, insulin sensitivity and lipogenesis, and broader integration of energy, lipid, and carbohydrate metabolism	Cardiovascular, metabolic, cancer, neurological	↑ FABP4, UCP1, AP2, PCK1, LPL, ADIPOQ, CD36, AQP7	Human:- Greene et al., 1995[59]

11.	Rev-erbAα / Rev-erbAα NR1D1	614	Chromosome 17 position q21[79]- M24898	m, hd	Heme	Rev-ERBα has roles in circadian rhythm in many processes, including adipogenesis. It is activated by heme as an inverse agonist	Neurological	↑ CYP7A, NFKBIA; ↓ ARNTL1, SERPINE1, APOA1, APOCIII, NR1D1, AFP	Human:- Miyajima et al., 1988[109]
12.	Rev-erbAβ / Rev-erbAβ NR1D2	579	Chromosome 3 at position p24.2[79]- L31785	m, hd	Heme	Rev-ERBβ has roles in circadian rhythm in many processes, including adipogenesis; heme activates Rev-ERBβ by inverse agonist	-	↑ SREBF1, CYP7A; ↓ ARNTL1, APOCIII, NR1D1, AFP	Human:- By Dumas et al., 1994;[41] Forman et al., 1994;[48] Retnakaran et al.,1994;[131] Enmak et al.,1994;[42] Pena de Ortiz et al., 1994;[121] Bonnelye et al., 1994[17]
13.	RAR-related orphan receptor-α / RORα NR1F1	523	Chromosome 15 position q21-q22[64] – U04897	m	Cholesterol, ATRA	RORα and RORβ have roles in circadian rhythm and cell survival; RORγ is involved in thymocyte development and homeostasis; melatonin activates RORα	-	↑IL6, IL17A, AFP, CYP19A1, CYP7B1, SREBF1, APOC3, ARNTL1,-CLOCK, CRY1, NPAS2, FGB, REV-ERBA, SULT-1E1(RORα); ARNTL1 (RORβ); ARNTL1 (RORγ); ↓OCN (RORα)	Human:- Becker-Andre et al., 1993[12]
14.	RAR-related orphan receptor-β / RORβ NR1F2	459	Chromosome 9 at position q22[6] – Y08639	m					Rat: Carlberg et al., 1994[25] Human : Exact data not known
15.	RAR-related orphan receptor-γ / RORγ NR1F3	560	Chromosome l at position q21[68,105] – Ul 6997	m					Human:- Hirose et al., 1994[68]

16.	Liver X receptor-α / LXRα NR1H3	447	Chromosome 11 at position p11.2 – U22662	RXR-h	Endogenous: Oxysterols	Cholesterol and steroid sensors with roles in lipid and carbohydrate metabolism	Metabolic	↑ SREBP1C, CYP7A1, ABC8, APOA1, APOE, LPL, PLTP	Rat:- Apfel et al.,1995[7] The clone was called RLD-1 (rat liver derived-1) Human:- Willy et al., 1995[166] and called LXRα (liver X receptor)
17.	Liver X receptor-β / LXRβ NR1H2	463	Chromosome 19 at position ql3.3[91] – U07132	RXR-h					Human (isolation):- Shinar et al. 1994[143] and called as NER, Rat (characterization):- Song et al. 1994[151] and called as UR (ubiquitous receptor) Human (Characterization):-Song et al., 1994[151] Mouse:- A processed but truncated LXRβ pseudogene was found in the mouse genome[3].
18.	Farnesoid X receptor / FXR NR1H4	476	Chromosome 12 at position q23.1 - BC130573.1	RXR-h	Endogenous: Bile acids (e.g., chenodeoxycholic acid) Dietary: Cafestol, guggulsterone	A sensor for bile acid that helps regulate bile acid homeostasis	Metabolic	↑ SLC10A2, ABCB1, ABCB11, NR0B2, HSD3B2, FETUB,ABCB4, FGF19, NOS2; ↓CYP7A1, HNF1A, HNF4A, SLCO1B1, SLC10A2	Rat:- Forman et al., 1995[49] Mouse:- Seol et al., 1995[140] and called RIP14 Human:- Papetti et al[120]. and called HRR-1. The sequence deposited in as a public database, but it has not been published till 2002

19.	Vitamin D receptor / VDR NR1I1	427	Chromosome 12cen-ql2[153,154]-J03258	RXR-h	Endogenous: Calcitriol (1′, 25′ dihdroxy vitamin D3) Clinical: Paracalcitol for secondary hyperparathyroidism in renal patients; Tacalcitol for psoriasis	Maintenance of serum calcium and phosphate levels for skeletal integrity; anti-proliferative in many tissues	Bone, cancer, cardiovascular,metabolic, immune and inflammatory, renal, neurological	↑ FGF23, CYP24A1, CALB1, BGLAP, SPP1; ↓ IL2, PHEX	Chicken:- McDonnell et al., 1987[104] Rat:- Burmester et al., 1988[24] Human:- Baker et al., 1988[11]
20.	Pregnane X receptor / PXR NR1I2	434	Chromosome 3 at position q12-q13.3 – AF061056	RXR-h	Endogenous: Bile acids Xenobiotic: St. John's Wort (hyperforin), Taxol, rifampicin, phenobarbital Dietary: Vitamin E, sulforaphane, Gugulipid	Metabolism and transport of pharmaceutical drugs, xenobiotics, and toxic bile acids in the liver and GI tract	Immune	↑ Multiple CYP2 and CYP3 gene family members, MDR1, MRP2, OATP2, UGT1A1, SULT, ↓ CYP7A1	Xenopus:- By Smith et al., 1994[150] and was called xONRl. Blumberg et al., 1998[15] and called BXR Mouse: - PXR (for Pregnane X Receptor) by Kliewer et al.,1998[77] Human:- SXR (for Steroid and Xenobiotic Receptor) by Blumberg et al. 1998a[16] . PXR by Lehmann et al., 1998[95]. PAR (for Pregnane Activated Receptor) by Bertilsson et al., 1998[13]

21.	Constitutive androstane receptor / CAR NR1I3	348	Chromosome 1 at position q23.3 Z30425	RXR-h	Endogenous: androstenol xenobiotics: Phenobarbital, DEHP, Meclizine	Metabolism of xenobiotics and endogenous lipids by regulating expression of cytochrome P450 genes	Involved in hepatotoxicity of acetaminophen	↑ CYP2B10, CYP311A, CYP3A4,CYP1A2, CYP2B6 THRSP, SLC21A6, MRP2, MDR1, OATP2	Human:- Baes et al., 1994[10]. It was first called MB67 and later CARα Mouse:- Choi et al., 1997[34]. It was called CARβ
22.	Hepatocyte nuclear factor-4-α / HNF4α NR2A1	465	Chromosome 20 at position ql2-ql3.1[40,168]-X76930	hd	fatty acids	Required for establishing and maintaining hepatocyte differentiation. HNF4α constitutively binds fatty acids	Metabolic	↑ LPIN1, SLC25A20, ABCC6, LIPC, COPA, HDAC6, RBKS, ERBB3, NGEF, ANXA4, LEAP2, EPO, G6PC (HNF4α)	Human:- Chartier et al., 1994[31]
23.	Hepatocyte nuclear factor-4-γ / HNF4γ NR2A2(alias NR2A3)	408	chromosome 8[40] – Z49826	hd					Human:- Drewes et al., 1996[40]
24.	Retinoid X receptor-α / RXRα NR2B1	462	Chromosme 9 at position q34.3[5,73] – X52773	hd	Endogenous: 9-cis retinoic acid	Embryonic cell patterning and organogenesis, cell proliferation and differentiation. Also functions as heterodimer with other nuclear receptors	Neurological and psychiatric, immune	↑↓ many genes as heterodimers with other receptors (e.g., LXRs, PPARs, FXR, TRs, RARs; ↑ ABC1 (with LXR); ↓ CYP7A1 (with FXR)	Mouse:- Hamada et al. 1989[63] Human:-Mangelsdorf et al., 1990[101]
25.	Retinoid X receptor-β / RXRβ NR2B2	533	Chromosome 6 at position p21.3[5] M84820	hd					Human:- Leid et al., 1992[96]
26.	Retinoid X receptor-γ / RXRγ NR2B3	463	Chromosome 1 band q22-23[5] – U38480	hd					Chicken:- Rowe et al., 1991[136] Human :- Mangelsdorfet al., 1992[100]

27.	Testicular receptor 2 / TR2 NR2C1	603	Chromosome 12 at position q22 – M29960 (isoform TR2-11)	hd, RXR-h	Orphan	Functions as negative modulators by suppressing the transcriptional activity of other NR members	NA	↑ POU5F1, NANOG, (TR2); ↑ POU5F1, NANOG, APOE, PCK2, CD36, LHCGR, BCL2, OXT (TR4); ↓ GATA1, HBB (TR2 and TR4)	Human:- Chang and Kokontis in 1988[30]
28.	Testicular receptor 4 / TR4 NR2C2	615	Chromosome 3 at position p25[94,170] – L27586	hd, RXR-h					Human: 1994. 1. Hirose et al[67] 2. Chang et al.[30] Mouse:- Law et al. 1994[89]
29.	Homologue of the Drosophila tailless gene / TLX NR2E1	385	Chromosome 6 at position q21[72] – Y13276	m, hd	Orphan	-	-	-	Drosophila:- Pignoni et al.,1990 Vertebrate:- Yu et al., 1994 and Monaghan et al., 1995[111,171] Human: Jackson et al., 1998[72]
30.	Photoreceptor cell specific nuclear receptor / PNR NR2E3	410	Chromosome 15 at position q24[62,78] – AF121129	m, hd	Orphan	-	-	-	Human:- Kobayashi et al., 1999[78] Mouse:- Chen et al., 1999[33]
31.	Chicken ovalbumin upstream promoter transcription factor I / COUP-TFI NR2F1	423	Chromosome 5 at position ql4[108] – XI2795	hd, RXR-h	Orphan	Diverse roles in the development of the peripheral nervous system, like early regionalization of neocortex, differentiation of subplate neurons, and guidance of thalamocortical axons	NA	↑ PCK1, PTH1R, CYP7A1, CYP11B2; ↓ LTF, LHCGR, APOA1, PENK, PPARA, SERPINC1, EPO, ACADL, NR0B1, OXT, OTC	Human:- Miyajima et al. 1988[108]. Wang et al. 1989[162]

32.	Chicken ovalbumin upstream promoter transcription factor II / COUP-TFII NR2F2	414	Chromosome 15 at position q26[86,127] – M64497	hd, RXR-h	Orphan	Roles in angiogenesis, establishing vein identity, vascular remodeling, and heart development	NA	↑ ANGPT1; ↓ ACOX1, CEBPA	Human:- Ladias and Karathanasis 1991[86]
33.	V-erbA-related / EAR-2 NR2F6	403	chromosome 19[108] – XI2794	m	Orphan	Functions include negative regulation of renin gene transcription and neuronal development	Cancer	↓ REN, LHCGR, ALDH2	Human:- Miyajima et al. 1988[110]
34.	Estrogen receptor-α / ERα NR3A1	595	Chromosome 6 position q25.1[106] – X03635	hd	Endogenous: 17β-estradiol Clinical: Mixed agonists (e.g. tamoxifen, NCOR1, NCOA3 raloxifene, and toremifene in breast cancer) Xenobiotics: Bisphenol A, PCBs	Regulation of cell growth and proliferation in multiple tissues (e.g., female reproductive tissues, bone, and CNS	Cancer, cardiovascular, immune and inflammatory, metabolic, neurological, reproductive	↑ MYC, NGF, BCL2, CXCL2, IGF1, TYMS; ↓ CD36, NDRG1, NCOR1, NCOA3	Human:- Green et al., 1986 and Greene et al., 1986[57,58]
35.	Estrogen receptor-β / ERβ NR3A2	477	Chromosome 14 at position q22-q24[42] – AB006590	hd					Human:- Ogawa et al., 1998[117]

36.	Estrogen-related receptor-α /ERRα NR3B1	521	Chromosome 11 at position q 12 – l3[33,142,145] – X51416	m, hd	Orphan	Structurally homologous to estrogen receptors; bind EREs but not activated by estrogens; modulate expression of enzymes involved in adipogenesis, energy metabolism, and synthesis of lipids, eicosanoids, and steroids	Bone, metabolic, deafness	↑ VEGF, PDK4, PLIN1, RB1CC1, BSP, CYP11A1, CYP27A1, HK2, PLSCR2, VLDLR, TFF1 (ERRα); CDKN1A (ERRβ); HK2, PLSCR2, VLDLR, CYP27A1, CDKN1A, CDKN1B, PDK4 (ERRγ)	Human:- Giguere et al., 1988[56]
37.	Estrogen-related receptor-β / ERRβ NR3B2	500	Chromosome 14 at position q24.3[33,142,145] AF094517	m, hd					Mouse:- Pettersson et al., 1996[124] Human:- Chen et al., 1999a[33]
38.	Estrogen-related receptor-γ / ERRγ NR3B3	436	Chromosome l at position q41[44] – AF058291	m, hd					Human:- Chen et al., 1999a; Eudy et al., 1998[33,34] Mouse: Hong et al., 1999[70]
39.	Glucocorticoid receptor / GR NR3C1	777	Chromosome5 at position q31-q32[51,156] – X03225	hd	Endogenous: Cortisol (hydrocortisone) Clinical: Fluticasone, dexamethasone and prednisolone in inflammatory disorders	Diverse developmental and physiological roles (e.g., antagonism of inflammatory signaling pathways, mediation of the stress response, and gluconeogenesis)	Metabolic, cardiovascular, immune and inflammatory, memory	↑ SCNN1A, GADD45B, GILZ, TAT; ↓ BGLAP, POMC, INS	Human:- Hollenberg et al., 1985[69]; Weinberger et al., 1985[165]
40.	Mineralocorticoid Receptor / MR NR3C2	984	Chromosome 4 at position q31.1[47,114] – Ml6801	hd	Endogenous: Aldosterone Clinical: Spironolactone in hypertensive cardiovascular disease	Regulating electrolyte and fluid balance in the kidney; specific roles in Central Nervous System	Metabolic	↑ SCNN1A, ATP1A1, ATP1B1, GILZ, SGK1, NDRG2	Human:- Arriza et al., 1987[8]

41.	Progesterone receptor / PR NR3C3	933	Chromosome 11 at position q22[103,135]. Another close location Chromosome 11 at position ql3 was also published[88] – Ml5716	hd	Endogenous: Progesterone Clinical: RU486 (Mifepristone) as an ANXA6 abortifacient	Diverse reproductive functions (e.g., establishing and maintaining pregnancy, developing breast tissue, and stopping proliferation in the uterus)	Cancer, metabolic, reproductive	↑ SERPINB14, FAS, MT2A, PGC, EGFR , IHH; ↓ ESR1, PGR, ANXA6	Human:- Misrahi et al., 1987[107]
42.	Androgen receptor / AR NR3C4	919	chromosome X at position q11-12[22] – M20132	hd	Endogenous: Testosterone, dihydrotestosterone Clinical: Flutamide and bicalutamide for prostate cancer and alopecia	Key role in male reproductive organs in addition to other systems (e.g., CNS)	Cancer, cardiovascular, immune, metabolic, neurological, reproductive	↑ MYC, VEGF, BCL2, IGF1, MUC1, P66(Shc), CCND1; ↓ TSHA, TSHB, PTEN, FAS, CASP2, CTNND2, ESR2, TMPRSS2	Human:- Lubahn et al., 1988[97]
43.	Nerve Growth factor IB / Growth factor inducible immediate early gene nur/77- like receptor / NGFIB/ Nur77 NR4A1	598	Chromosome 12 at position q13 - L13740	m, hd, RXR-h	Orphan	Apoptotic signaling in thymocytes and tumor cells; signaling in the hypothalamic-pituitary axis. Bone marrow differentiation and the survival of Ly6C– monocytes	Cancer	↑ APOA5, SERPINA3, TCL1A, INSL3, UCP3, CD36, ADIPOR2, SLC2A4, CAV3, POMC, HSSD3B2, FABP5, GJA1, TLL1, WISP2, IKBKE	Human:- Chang et al., 1989[29]
44.	Nuclear receptor related 1 / NURR1 NR4A2	598	Chromosome 2 position at q22-q23 [26,98,158]– X75918	m, RXR-h	Orphan	Expression is induced in response to various stress stimuli and growth factors; contributes to development of dopaminergic neurons.	Neurological, cardiovascular	↑ INSL3, TH, FABP5, SLC18A2, SLC6A3, DLK1, PTPRU, KLH1, IKBKE; ↓IL1B,IL6, IL8,CCL2,CCL3, CCL4,TNFA, INOS	Human:- Mages et al., 1994[98]

45.	Neuron-derived orphan receptor 1 / NOR1 NR4A3	626	Chromosome no. 9 position at q22[85] – D78579	m	Orphan	Expression is induced in response to various stress stimuli and growth factors; signaling roles in multiple tissues, including the hypothalamic-pituitary Axis	Cancer	↑ INSL3, FABP5, CCND1, CCND2, IKBKE	Human:- Labelle et al., 1995;[85] Hedvat and Irving 1995[66]
46.	Steroidogenic factor 1 / SF1 NR5A1	461	Chromosome 9 at position q33[167] – U76388	m	Phosphatidylinositols	Regulates mammalian sexual development; controls differentiation of steroidogenic tissues	Endocrine, Metabolic	↑ STAR, CYP11A1, HS3DB2, INHA, AMH, CYP19A1	Human:- Wong et al. 19961[67]
47.	Liver Receptor Homolog-1 / LRH-1 NR5A2	500	Chromosome l at position q32[52] – U93553	-	Phosphatidylinositols	Regulates genes involved in steroid, bile acid, and cholesterol homeostasis; drives reprogramming of somatic cells to iPS cells	NA	↑ POU5F1, NANOG, TBX3, KLF2, KLF5, RBP4, CYP17A1, CYP11A1, CYP7A1, CYP8B1, ABCB11, APOM, FAS	Human:- Galarneau et al., 1998[52]
48.	Germ cell nuclear Factor / GCNF NR6A1	480	Chromosome 9 at position q33-34.1[2] – Q15406 (Uniprot)	hd	Orphan	Transcriptional repressor. An essential factor in vertebrate embryogenesis	NA	↓ POU5F1, NANOG, PPARD, TDGF1, TDGF3, PRM1, PRM2, BMP15, GDF9, CYP26A1,TDGF1	Human:- Siisens and Borgmeyer 1996[144]

* m= monomer; hd= homodimer; RXR-h=heterodimer with RXR

Table 2. Pseudo-nuclear receptors found in humans

S.N.	Name	Abbreviation	NRNC Symbol	Chromosomal location	Type	References
1.	Farnesoid X Receptor, beta	FXRβ	NR1H5	chr1+:114480335	Unprocessed	Maglich et al., 2001; Otte et al., 2003[99,119]
2.	Hepatocyte Nuclear Factor 4, gamma	HNF4γ	NR2A2	chr13—:55510764	Processed	Tchenio et al., 1993[155]
3.	Estrogen-related receptor, alpha	ERRα	NR3B1	chr13—:19064728	Processed	Sladek et al., 1997[147]

responsible for embryonic development, reproduction, immune function and metabolic homeostasis[46]. NRs, by binding directly to hydrophobic ligands (including fatty acids, fat-soluble hormones, vitamins, dietary lipids, bile acids, oxysterols, heme and xenobiotic compounds), can regulate gene expression programs in a variety of tissues and cell-types[134,146,176]. It is interesting to note that many small lipophilic compounds like steroids, retinoids, thyroid hormones and vitamin D3 etc. (which act as cognate ligands for specific NRs) were identified and purified based on their physiological functions, long before they were identified as ligands of NRs. In the initial years this superfamily was named as 'Nuclear Hormone Receptor' family or superfamily as the initial receptors to be cloned included only steroid/hormone receptors (GR, ER etc.). Later it was clear that all cognate ligands are not always steroids / hormones, which lead to their present nomenclature as 'Nuclear Receptors' (NR) which has now global acceptance[146]. The review presented herein in form of a compendium, deals primarily with the established basic facts and information about the NR superfamily and is confined mainly to humans. In human genome, three NR pseudogenes have also been identified so far (Table 2). Of these three, FXRβ is found in the unprocessed form. Reports reveal that FXRβ may be imparting hitherto unknown functions in cholesterol metabolism along with FXR[119].

2. General Structural and Functional Organization of Nuclear Receptors

Members of Nuclear receptor superfamily share a common structural and functional organization which is the true characteristic of this superfamily. NRs in general are composed of 5-6 defined regions (A-F; originally defined) that have modular characters as depicted in Fig. 1 and briefly described below[80]. NRs have a highly variable (both in size and sequence) N-terminal domain (NTD), a highly conserved DNA binding domain (DBD) responsible for binding to the response element, a highly variable hinge region, and a domain dedicated for ligand binding (LBD). Many NRs are also reported to contain a variable domain named as F-domain at their C-terminus.

2.1 N-Terminal Domain (NTD, Amino-Terminal Domain or Region A/B)

This region encompasses one (or sometimes more) autonomous transcriptional activation function (AF-1), that can function constitutively in a ligand-independent manner and activate basal transcription, when connected to a heterologous DNA binding domain[163]. However, steroid receptors have been suggested to have a silent AF-1 when not bound to their cognate ligands. When comparing different subfamilies and groups of NRs, A/B domain shows the least evolutionary sequence conservation within different subfamilies and groups. It is difficult to have a distinction between the regions A and B. The length of this N-terminal regulatory domain differs significantly which ranges from 23 amino acid residues in case of vitamin D receptor (NRIII), to 550 amino acid residues in case of androgen (NR3C4), mineralocorticoid (NR3C2) and glucocorticoid receptors (NR3C1). However, to produce a strong modulation of target gene expression, AF-1 synergistically acts along with AF-2 which is present in the LBD (Ligand Binding Domain) of the NRs.

2.2 The DNA-Binding Domain (DBD or Region C)

This domain is most conserved in different family and subfamilies of NRs and is responsible for sequence-specific DNA recognition. Due to its unique response element recognition and dimerization properties, this domain has been a major focus of investigation by many researchers. Many studies related to DBD of NRs yielded numerous X-ray, nuclear magnetic resonance (NMR) and protein crystallization data in their DNA complexed and un-complexed forms. The DBD is comprised of two zinc-finger motifs, the N-terminal motif Cys-X2-Cys-X13-CysX2-Cys (C-I) and the C-terminal motif Cys-X5-Cys-X9-Cys-X2-Cys (C-II) (Figure 1). Each zinc-finger has four cysteine residues that chelate one Zn^{2+} ion. In addition, the DBD encompasses several sequence elements (termed P-, D-, T- and A-boxes) that have now been characterized, and these define: (i) specificity of the response element (ii) an interface for dimerization and (iii) interaction with the DNA and (iv) DNA core recognition sequence. DBD in most of the NRs contains a nuclear localization sequence (NLS) and also a nuclear export signal (NES). This has been shown in case of GR, ER, AR, LXR, RXR, PR, RAR, RevErb, TR and VDR[14]. However, some exceptions like PXR and CAR having a leucine-rich NES in their LBD is also reported[74].

2.3 Hinge Region (Region D)

This region of NRs is relatively less conserved in comparison to the surrounding highly structured regions C and E. This domain primarily functions as a 'hinge' between the C and E domains and hence can be termed as 'Hinge region'. It appears to execute cellular compartmentalization functions by exerting its function by helping DBD and LBD to overcome steric hindrance and adopting different conformational changes. To be precise, this region confers conformational flexibility to the receptor. Thus, it indirectly helps regions C and E to contribute dimerization interfaces by allowing some receptors to accommodate their specific heterodimeric partners and response elements for transactivation of the target gene. Region D further contains Nuclear Localization Signal (NLS) or potential Nuclear Export Signal (NES) which contribute to the nucleo-cytoplasmic shuttling of the receptor[14,61,160]. The visible intracellular localization of NRs thus will be a consequence of a dynamic equilibrium between the operational strengths of these localization signals[82].

2.4 Ligand Binding Domain (LBD or Region E)

The ligand-binding domain (LBD/the region E) can be regarded as the hallmark of a NR as it is highly structured, and translates a wealth of distinct physiological functions, mostly operated in a ligand-dependent manner. Among the various NRs, this domain is moderately conserved in sequence but highly conserved in its structure. It can be regarded as the second most conserved region after DBD[23]. The LBD also serves as a major binding site for different coactivators and corepressors. The LBD contains the ligand-dependent activation function AF-2 that acts as a major dimerization interface and often has a repression function[60,27,159,113]. Crystal structures of the region E (LBD) alone or in bound state with agonists, antagonists and coregulator peptides helped studying the detailed mode of action of NRs. Unliganded RXRα (NR2B1), the all-trans retinoic acid-bound RARγ (NR1B3) and the agonist-bound thyroid receptor TRβ (NR1A2) are the three NRs whose 3D structures were reported initially[19,130,161]. Among all the domains of NRs, the LBD contributes most for the receptor dimerization process.

2.5 Carboxy-Terminal (F-domain)

The F domain is found at the C-terminus of the LBD in only some of the NRs and exhibits least evolutionary conservation. The length varies from smaller to much longer as in the cases of, estrogen (NR3A) and retinoic acid (NRIB) receptors. The function of this C-terminal sequence is still ambiguous. Some studies advocate that this region plays a part in coactivator recruitment to the LBD and in determining its specificity[122,145]. It was also observed that this domain inherits very little structural features. It is also speculated that this domain 'fine tunes' the molecular events related to the transcriptional properties executed via the LBD, or the whole receptor[112,115].

3. Diversity of Nuclear Receptors

NRs form a large superfamily of phylogenetically related proteins, with 21 genes in case of *Drosophila melanogaster*[1], 48 in humans[132] with one more, FXRβ, in the mouse[133]

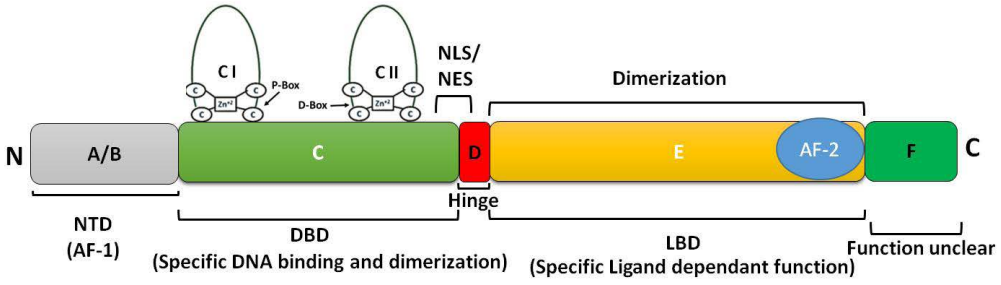

Figure 1. A general structural and functional organization of nuclear receptors. *Different letters starting from A (N-terminus) and ending with F (C-terminus) signify different structural and functional domains whose details are explained in the text. A/B refers to N-terminal domain (NTD), C refers to DNA binding domain (DBD), D refers to Hinge region, E refers to Ligand binding domain (LBD) and F shown at the C-terminus is absent in most of the receptors.*

which all together number 70. The nematode worm *Caenorhabditis elegans* unexpectedly has more than 270 genes and remains a biological anomaly[148] (Table 3).

Table 3. Numbers of Nuclear Receptors found in different species*

Name of species	Common Name	No. of nuclear receptors
Amphimedon queenslandica	A type of Sponge	2
Mnemiopsis leidyi	A type of ctenophore	2
Trichoplax adhaerens	A type of placozoan	4
Nematostella vectensis	A type of cnidarian	17
Caenorhabditis elegans	A type of nematode	270
Homo sapiens	Human	48
Mus musculus	Mice	49
Rattus rattus	Rats	47

* Compiled from different source references

In a joint effort, this enormous diversity has been well-organized in a phylogeny-based nomenclature system (Nuclear Receptors Nomenclature Committee, 1999) in the form of NRxyz, where 'x' represents the sub-family, 'y' the group and 'z' represents the gene. Along with the NRs that have DBD and LBD, sub-family NR0 contains atypical NRs lacking either of these two domains and are not represented in the phylogenetic tree. These include Knirps, KNRL and EGON (NR0A1, 2, 3) in case of *Drosophila*, DAX1 and SHP (NR0B1, 2) in vertebrates (Table 1). Out of nearly 70 NRs identified in insects, birds and animals till date only some (less than half) have been assigned true ligands. Others are referred to as 'orphan receptors'. Out of these 'orphan receptors' whose intrinsic ligands have been subsequently identified are grouped in 'adopted receptors'[23].

3.1 Classification of NRs

NR superfamily members have been classified or grouped in several ways . However, the superfamily can be conveniently divided into four subfamilies based on DNA-binding properties and dimerization preferences. The first subfamily comprises of group I receptors which mostly forms 'homodimers'. It includes the classical steroid receptors like GR, MR, PR, AR, ER etc. The members that function as 'heterodimers' with RXR form the groups II and III. The group II consists of receptors whose ligands have been identified and group III includes the 'orphan receptors'. The 'monomers' form the group IV.

3.2 Mode of Action

Classically, NRs act in three major steps: repression, de-repression and transcription activation[87]. Repression is typical in cases of apo-NRs that employ corepressor complex with Histone Deacetylase Activity (HDAC). Ligand binding follows de-repression, which involves dissociation of this complex and recruitment of the coactivator complex, with Histone Acetyltransferase (HAT) activity. HAT activity results into chromatin de-condensation, which is required but is not fully sufficient alone for activation of the target gene. Subsequently, the HAT complex dissociates and a second coactivator complex is assembled (TRAP/DRIP/ARC), which is able to launch the basal transcription machinery, and hence start the transcriptional activation of the target gene (Figure 2). However, a few NRs may act even in the absence of the ligand, whereas most others cannot.

When considered in subgroups, other specific modes of action of NRs are also projected; i) that of Steroid Hormone Receptors (SHRs), ii) that of retinoid/thyroid/vitamin D receptors[50,75,149].

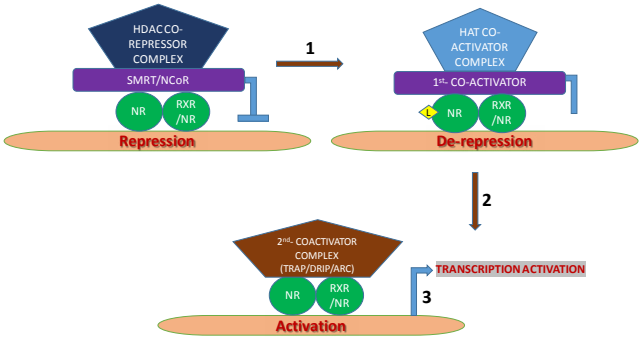

Figure 2. A three step mechanism of NR activation. *'L' represents Ligand.*

CLASS-I: Steroid Hormone Receptors (SHRs) like GR, ER AR, PR and MR in the absence of their respective ligands remain sequestered in a large multi-protein complex having the receptor, heat shock protein-90 (HSP90), Hsp70, FKBP52/51 and some other proteins. The exact cellular localization of this large complex is sometimes controversial and mainly depends on the type of the cell and physiological states. However, the general consensus has been that unliganded SHRs are mainly localized in cytoplasm of the cell. Upon interaction with

their specific hormone there is a distinct change in the conformation of the receptor structure and the process of signal transduction starts with the onset of nuclear translocation. Specifically, in case of GR, AR, MR, PR, hormone binding leads to dissociation of HSPs and other associated proteins resulting in the release of the monomeric receptor from the cytoplasmic retention complex. As a result nuclear translocation is initiated and the SHRs become competent to associate as homodimers onto the specific sites of DNA (Figure 3)

CLASS-II: In contrast to the above mechanism, TR, RAR and VDR do not interact as efficiently with HSPs and are localized mostly in the nucleus even in the absence of their specific ligands. Some unliganded NRs of this class may act as transcription repressors by binding to the target DNA along with corepressor proteins. On the contrary, Constitutive Androstane Receptor (CAR) as an exception is reported to remain transcriptionally active even in the absence of its ligands[36]. This class of NRs also follows the rule of hormone-induced conformational changes which supports the theory that the conformation change of NRs by their respective ligands is the key step in the transcription activation pathway. The TR, RAR, PPAR, PXR, CAR and VDR can utilize RXR as a heterodimeric partner in their mode of actions (Figure 4). The contact with the DNA depends on specific sequences within the DBD, namely the proximal (P-box) and distal (D-box) and the zinc finger motifs. The half-site recognition is determined by the P-box whereas the spacing between half-sites is determined by D-box (Figure 1).

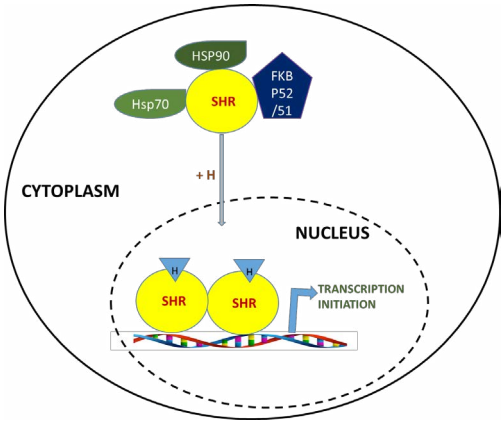

Figure 3. Schematic diagram showing the mechanism of activation of a typical homodimeric Steroid Hormone Receptor (SHR). *'H' represents Hormone.*

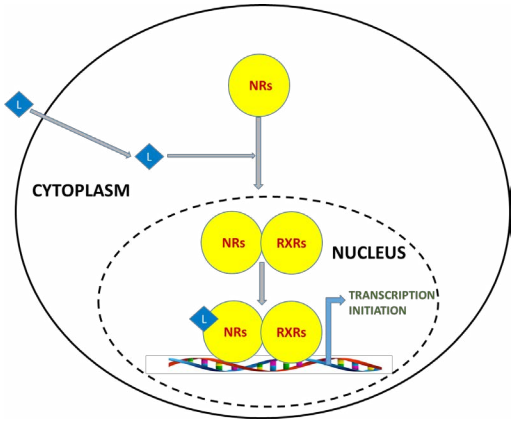

Figure 4. Schematic diagram showing activation mechanism for a typical heterodimeric NR complexed with RXR .*' L' represents Ligand.*

Both classes of NRs (heterodimers and monomers) upon activation can bind to their target DNA and recruit coactivators. This DNA bound NR complex can now act as a substrate for transcription initiation. The sequence AGGTCA acts as common consensus sequence with a few variations for the response element of most of the NRs. For dimeric NRs, Hormone Response Elements (HREs) are composed of two repeats of the consensus sequence separated by small but variable numbers of non-consensus nucleotides. Response element consensus sequences can variably exist as direct repeats (AGGTCA...AGGTCA) for heterodimers, inverted repeats (AGGTCA...ACTGGA) or everted repeats (ACTGGA...AGGTCA) for homodimers[23]. The monomeric receptor (e.g. ERR) binds the half-site sequence AGGTCA (Figure 5).

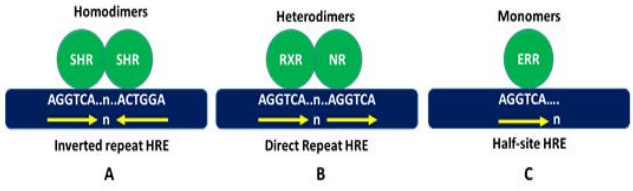

Figure 5. Schematic diagram showing different NR dimerization and alignments of DNA binding sequences. *A. homodimeric NRs (inverted repeat HRE), B. RXR heterodimers (direct repeat HRE) and C. monomeric NR (half-site HRE). Arrows shows the consensus NR recognition sequence AGGTCA.*

3.3 Nuclear Receptors as Drug Targets

NRs have many vital roles in pathologies which

make them a suitable target for drug discovery and development. Presently, NRs act as targets for about 15 percent of all available pharmaceuticals ranging from endocrine-related cancers, many metabolic disorders to oral contraceptives. Among the NRs, the most common targets are the estrogen receptors, glucocorticoid receptors and progesterone receptors. They all work by similar mechanism i.e. the natural ligand and the drug molecule compete for the same binding site thereby influencing the overall performance of the receptor. The major pathological conditions where NRs act as drug targets include asthma, COPD, diabetes type II, hyperlipidemia, contraception, hormone replacement therapy, endocrine-related cancers like breast / prostate cancers, and osteoporosis etc. This undoubtedly infers NRs as a central class of targets for pharmaceutical development. Among 48 human NRs, Pregnane and Xenobiotic Receptor (PXR, NR1I2) and Constitutive Androstane Receptor (CAR, NR1I3) are the primary transcriptional regulators of the genes responsible for the metabolism of endobiotics and xenobiotics including elimination of drugs, drug metabolites, herbals and dietary constituents[45,126]. Vitamin D Receptor (VDR, NR1I1), which is well-known for its role in calcium and phosphate homeostasis, is believed to transcriptionally induce drug metabolizing enzymes and drug transporters, especially in the enterocytes of the intestinal tissues. Similarly, the Farnesoid X Receptor (FXR, NR1H4); Liver X Receptor (LXR-α, NR1H3); Peroxisome Proliferator Activated Receptor (PPAR-α, NR1C1), and Retinoid-related Orphan Receptors (ROR-α, ROR-γ) also play central roles in regulating genes associated with drug absorption, distribution, metabolism and Excretion (ADME) in certain specialized conditions. Hepatocyte Nuclear Factor alpha (HNF4-α, NR2A1), executes a synergizing role in PXR- and CAR-mediated transactivation of drug metabolizing enzymes and transporter-encoding genes. Cytochromes P450 (CYP), which are primarily regulated by NRs, serve as a chief source of variability in individual drug pharmacokinetics and drug response, and thus making NRs as an important drug target[128,174].

3.4 Nuclear Receptors as Epigenetic Marks

Epigenome refers to the states of potentially heritable epigenetic changes across the genome[157]. It can also be regarded as the center stage for adaptive responses to the external stimuli. Recently, it has been observed that during mitosis certain NRs associate with the chromosomes and co-migrate with condensing chromatin. It is suggested that by this mechanism the cells naturally inherit a 'biomolecular blueprint' of bound transcription factors over to next generations to express and sustain their characteristic proteome. Thus, cells sustain their self-renewal potency via mitosis by ensuring that the characteristic proteome and traits are distinctively preserved for their progeny during this transition phase. This mechanism, although somewhat analogous to 'epigenetic marking', differs in nature since transcription factors themselves execute this transmission. To uphold the mechanistic distinctions, the occurrence of the phenomenon has been been explained by the BIOPIT (biomolecular imprints offered to progeny for inheritance of traits) model. The BIOPIT model proposed attempts to explain how the disruption of this event by therapeutic anti-hormones or endocrine disruptors over prolonged periods may lead to eradication of 'cellular transcription memory' with potentially deleterious consequences[83,134].

4. Conclusion and Future Perspective

NRs represent a superfamily of transcription factors (48 in humans) which regulate the expression of a large variety of important genes involved in normal functioning and pathogenesis of a variety of diseases which gives them a special status in drug development. A thorough insight into the understanding of the regulation of NRs, their tissue-expression profile and involvement of co-factors, will definitely help us to address many queries related to therapeutic efficiency and individual variations in response to drug molecules. Therefore, discovery and designing of NR-specific ligands with well-demarcated functions are the current focus in NR-based drug discovery.

Future studies in the field of NRs should focus on their different post-transcriptional modifications like acetylation, phosphorylation and SUMOylation and the effects and diverse inter- or intra-molecular interactions which result in receptor activation or repression, and finally, discovery of ideal candidate drug molecules. Another important area includes orphan receptors whose endogenous ligands are still unclear, whereas there are many endogenous ligands and clinically used drugs

whose suitable receptors are unknown. So, the future focus of investigations should be to identify the ligands, or more precisely Selective Nuclear Receptor Modultors (SNuRMs) that have preferred clinical importance.

5. Acknowledgements

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