SnapShot: Nuclear Receptors I

Neil J. McKenna and Bert W. O'Malley
Baylor College of Medicine, Houston, TX 77030, USA

Cell

Receptor/ Family*	Symbols	Ligands	Major Functions	Disease Associations	Target Genes
Estrogen receptors*	ERα/NR3A1; ERβ/NR3A2	Endogenous: 17β-estradiol Clinical: Mixed agonists (e.g. tamoxifen, 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*
Androgen receptor	AR/NR3C4	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*
Glucocorticoid receptor	GR/NR3C1	Endogenous: Cortisol (hydrocortisone) Clinical: Fluticasone and prednisolonein 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*
Vitamin D receptor	VDR/NR1I1	Endogenous: Calcitriol (1′,25′ dihdroxy vitamin D3) Clinical: Paracalcitol for 2° hyperparathyroidism in renal patients; Tacalcitol for psoriasis	Maintenance of serum calcium and phosphate levels for skeletal integrity; antiproliferative in many tissues	Bone, cancer, cardiovascular, metabolic, immune and inflammatory, renal, neurological	↑ *FGF23*, *CYP24A1*, *CALB1*, *BGLAP*, *SPP1*; ↓ *IL2*, *PHEX*
Thyroid hormone receptors*	TRα/NR1A1; TRβ/NR1A2	Endogenous: Thyroxine (T4),Triiodothyronine (T3) Clinical: Levo-thyroxine, triiodothyroacetic acid (TRIAC) in resistance to thyroid hormone	Regulation of oxygen consumption; protein, carbohydrate, lipid, and vitamin metabolism	Thyroid conditions, cancer	↑ *ADRB1*, *PCK2*, *GH1*, *UCP1*; ↓ *DIO2*, *EHHADH*, *PRL*, *EGFR*
Progesterone receptor	PR/NR3C3	Endogenous: Progesterone Clinical: RU486 (Mifepristone) as an 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*
Mineralocorticoid receptor	MR/NR3C2	Endogenous: Aldosterone Clinical: Spironolactone in hypertensive cardiovascular disease	Regulating electrolyte and fluid balance in the kidney; specific roles in the CNS	Metabolic	↑ *SCNN1A*, *ATP1A1*, *ATP1B1*, *GILZ*, *SGK1*, *NDRG2*
Peroxisome-proliferator-activated receptor-γ	PPARγ/NR1C3	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*
Peroxisome-proliferator-activated receptor-α	PPARα/ NR1C1	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*
Peroxisome-proliferator-activated receptor-δ (β)	PPARδ/ NR1C2	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*
Retinoic acid receptors*	RARα/NR1B1; RARβ/NR1B2; RARγ/NR1B3	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*
Liver X receptors*	LXRα/NR1H3; LXRβ/NR1H2	Endogenous: Oxysterols	Cholesterol and steroid sensors with roles in lipid and carbohydrate metabolism	Metabolic	↑ *SREBP1C*, *CYP7A1*, *ABC8*, *APOA1*, *APOE*, *LPL*, *PLTP*
Retinoid X receptors*	RXRα/NR2B1; RXRβ/NR2B2; RXRγ/NR2B3	Endogenous: 9-*cis* retinoic acid	Embryonic cell patterning and organogenesis, cell proliferation and differentiation, other functions as heterodimers 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)
Pregnane X receptor	PXR/NR1I2	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*
Constitutive androstane receptor	CAR/NR1I3	Endogenous: Androstanol, 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*
Farnesoid X receptor	FXR/NR1H4	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*

See online version for legend and references.

SnapShot: Nuclear Receptors I

Neil J. McKenna and Bert W. O'Malley
Baylor College of Medicine, Houston, TX 77030, USA

Cell

Nuclear receptors (NRs) are a superfamily of transcription factors regulated by the direct binding of endogenous, dietary, clinical, and xenobiotic ligands. NRs are defined by the presence of conserved zinc finger DNA- and/or ligand-binding regions. NRs interact with a group of diverse factors named coregulators (i.e., coactivators and corepressors) to orchestrate programs of gene expression in specific tissues. Cell signaling pathways also can regulate NRs and their coregulators.

In this SnapShot, we present information on the endocrine nuclear receptors and the adopted orphan receptors. The endocrine receptors are activated by small and predominantly lipophilic ligands of the endocrine system, many of which have well known physiological roles. This subgroup consists of the first seven receptors in the chart: the estrogen (ER), androgen (AR), glucocorticoid (GR), vitamin D (VDR), thyroid (TR), progesterone (PR), and mineralocorticoid (MR) receptors. Adopted orphan receptors are a subgroup for which cognate ligands were uncharacterized at the time of their cDNA cloning but have since been identified. This group includes the last fourteen receptors in the chart: peroxisome-proliferator-activated (PPAR), retinoic acid (RAR), liver X (LXR), retinoic X (RXR), pregnane X(PXR), constitutive androstane (CAR), and farnesoid X (FXR) receptors. The ordering in the table is based on visits to the Nuclear Receptor Signaling Atlas (NURSA) Molecule Pages from May 2009 to May 2010.

The table includes information about NR ligands, target genes, functions, and disease associations. Although human gene names are shown (familiar name/Nuclear Receptor Nomenclature Committee name), regulation may have been demonstrated in human, mouse, or rat cells or tissues. In certain cases, subfamily members that are encoded by distinct genes are discussed collectively. However, each receptor has specific contributions to the endocrine signaling axis in question. Additional information, such as expression, knockout phenotypes, transcriptomics, cistromics, proteomics, and specific references for disease associations, is available at the NURSA Molecule Pages (http://www.nursa.org) and in the selected further reading provided below.

Abbreviations

CNS, central nervous system; DEHA, Bis(2-ethylhexyl) adipate; DEHP, Bis(2-ethylhexyl) phthalate; GI, gastrointestinal; FAs, fatty acids; PCBs, polychlorinated biphenyls; PUFAs, polyunsaturated fatty acids.

ACKNOWLEDGMENTS

The support of the NURSA Bioinformatics Resource in curating this information is gratefully acknowledged. N.J.M. and B.W.O. are supported by NIH U19-DK62434. The authors regret the omission of many important contributions to this field as a result of space constraints.

REFERENCES

Flamant, F., Baxter, J.D., Forrest, D., Refetoff, S., Samuels, H., Scanlan, T.S., Vennström, B., and Samarut, J. (2006). International Union of Pharmacology. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. Pharmacol. Rev. *58*, 705–711.

Heldring, N., Pike, A., Andersson, S., Matthews, J., Cheng, G., Hartman, J., Tujague, M., Ström, A., Treuter, E., Warner, M., and Gustafsson, J.A. (2007). Estrogen receptors: how do they signal and what are their targets. Physiol. Rev. *87*, 905–931.

Mark, M., Ghyselinck, N.B., and Chambon, P. (2009). Function of retinoic acid receptors during embryonic development. Nucl. Recept. Signal. *7*, e002.

Moore, D.D., Kato, S., Xie, W., Mangelsdorf, D.J., Schmidt, D.R., Xiao, R., and Kliewer, S.A. (2006). International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnene X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. Pharmacol. Rev. *58*, 742–759.

Nuclear Receptors Nomenclature Committee. (1999). A unified nomenclature system for the nuclear receptor superfamily. Cell *97*, 161–163.

Pyper, S.R., Viswakarma, N., Yu, S., and Reddy, J.K. (2010). PPARalpha: energy combustion, hypolipidemia, inflammation and cancer. Nucl. Recept. Signal. *8*, e002.

Scarpin, K.M., Graham, J.D., Mote, P.A., and Clarke, C.L. (2009). Progesterone action in human tissues: regulation by progesterone receptor (PR) isoform expression, nuclear positioning and coregulator expression. Nucl. Recept. Signal. *7*, e009.

Sonoda, J., Pei, L., and Evans, R.M. (2008). Nuclear receptors: decoding metabolic disease. FEBS Lett. *582*, 2–9.

Tontonoz, P., and Spiegelman, B.M. (2008). Fat and beyond: the diverse biology of PPARgamma. Annu. Rev. Biochem. *77*, 289–312.

Zhou, C., Verma, S., and Blumberg, B. (2009). The steroid and xenobiotic receptor (SXR), beyond xenobiotic metabolism. Nucl. Recept. Signal. *7*, e001.

  DOI 10.1016/j.cell.2010.08.026