The super-family of nuclear receptors
The super-family of nuclear receptors

- The largest TF family of metazoan trx regulators
- Signal responsive factors
  - mediate transcriptional response to complex extracellular signals
- Short signal transduction pathway
  - lipophilic signalling molecules $\rightarrow$ TF $\rightarrow$ transcriptional response
  - classical steroid hormones secreted from endocrine cells $\rightarrow$ transported by the blood $\rightarrow$ target cell $\rightarrow$ diffuse into the cells $\rightarrow$ bind receptor $\rightarrow$ activated $\rightarrow$ modulate target genes

In the genome of the worm *C. elegans*, the nuclear receptors constitutes the largest family of TFs with more than 200 members. In the human genome we have so far identified 48 nuclear receptors.
Ligand responsiveness

- **lipophilic hormone ligands**
  - Can pass the lipid layer in the cell membrane
  - Activating ligand can be generated in three ways:
    - Synthesized in a remote endocrine cell (e.g., thyroid hormone)
    - Made in the target cell from an apohormone (e.g., 9-cis-retinoic acid)
    - Metabolite synthesized intracellularly in the target cell (e.g., prostaglandines)
  - Classical model:
    - Hormone + inactive receptor $\Rightarrow$ allosteric change $\Rightarrow$ active receptor binds DNA and modulate transcription

- **Ligand-binding domain - LBD**
  - LBD - a molecular switch which upon ligand binding changes the receptor into a transcriptional active form
Common design

- A/B domain
- DNA-binding (C) domain
- Hinge (D) domain
- Ligand-binding (E) domain
- Autonomous activation functions
Common structures with multiple sub-domains

- **A/B**: variable, constitutive activator function AF-1
  - N-terminal domain variable in sequence/length having activator function (AF-1)

- **C**: conserved DBD
  - with two C4-zinc fingers which also mediate dimerization

- **D**: hinge
  - variable hinge-region often carrying an NLS

- **E**: ligand binding domain LBD, ligand-dependent AF-2
  - conserved larger ligand-binding domain (LBD) functionally complex
  - ligand-binding, hsp interaction, dimerization, NLS

- **F**: variable C-term
  - Variable C-terminal domain without specific function
Functional domains

- **DBD**
  - mediate binding to a hormone responsive element (HSE)
  - 2 conserved zinc fingers
TAD = AF1 and AF2
NR function = Activators and repressors

Activation

A Ligand-dependent Transactivation

Repression

B Active Repression

C Ligand-dependent Coactivation

D Ligand-dependent Transrepression
Classification - subfamilies

- **Type I: Steroid receptors**
  - undergo nuclear translocation upon ligand activation
  - bind as homodimers to inverted repeat DNA half sites,

- **Type II: RXR heterodimers**
  - retained in the nucleus regardless of the presence of ligand
  - usually bind as heterodimers with RXR to direct repeats.

- **Type III: orphan NRs**
  - dimeric orphan receptors
  - Monomeric orphan receptors
  - Half receptors
## Alternative classifications

**Evolutionary analysis of the receptors has led to a subdivision in six different subfamilies**

### RXR heterodimers

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtype</th>
<th>Denomination</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>PXR</td>
<td>α, β</td>
<td>Pregnan X receptor</td>
<td>Pregnanes; C21 steroids</td>
</tr>
<tr>
<td>CAR/MB67</td>
<td>α, β</td>
<td>Constitutive androstan receptor</td>
<td>Androstanes; 1,4-bis(3,5-dichloropyridyloxy)]benzene</td>
</tr>
<tr>
<td>LXR</td>
<td>α, β</td>
<td>Liver X receptor</td>
<td>Oxyesters</td>
</tr>
<tr>
<td>FXR</td>
<td>α, β</td>
<td>Farnesoid X receptor</td>
<td>Bile acids</td>
</tr>
<tr>
<td>RevErb</td>
<td>α, β</td>
<td>Reverse ErbA</td>
<td>Unknown</td>
</tr>
<tr>
<td>RZR/ROR</td>
<td>α, β, γ</td>
<td>Retinoid Z receptor/retinoic acid-related orphan receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>RXR</td>
<td>α, β, γ</td>
<td>Retinoid X receptor</td>
<td>9-Cis-retinoic acid</td>
</tr>
<tr>
<td>COUP-TF</td>
<td>α, β, γ</td>
<td>Chicken ovalbumin upstream promoter transcription factor</td>
<td>Unknown</td>
</tr>
<tr>
<td>HNF-4</td>
<td>α, β, γ</td>
<td>Hepatocyte nuclear factor 4</td>
<td>Fatty acyl-CoA thioesters</td>
</tr>
<tr>
<td>TLX</td>
<td>α, β, γ</td>
<td>Tailles-related receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>PNR</td>
<td></td>
<td>Photoreceptor-specific nuclear receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>TR2</td>
<td>α, β</td>
<td>Testis receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class II</td>
<td>RXR</td>
<td>Retinoid X receptor</td>
<td>9-Cis-retinoic acid</td>
</tr>
<tr>
<td>Class II</td>
<td>COUP-TF</td>
<td>Chicken ovalbumin upstream promoter transcription factor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class II</td>
<td>HNF-4</td>
<td>Hepatocyte nuclear factor 4</td>
<td>Fatty acyl-CoA thioesters</td>
</tr>
<tr>
<td>Class II</td>
<td>TLX</td>
<td>Tailles-related receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class II</td>
<td>PNR</td>
<td>Photoreceptor-specific nuclear receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class II</td>
<td>TR2</td>
<td>Testis receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class III</td>
<td>GR</td>
<td>Glucocorticoid receptor</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Class III</td>
<td>AR</td>
<td>Androgen receptor</td>
<td>Androgens</td>
</tr>
<tr>
<td>Class III</td>
<td>PR</td>
<td>Progesterone receptor</td>
<td>Progestins</td>
</tr>
<tr>
<td>Class III</td>
<td>ER</td>
<td>Estrogen receptor</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Class III</td>
<td>ERR</td>
<td>Estrogen-related receptor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class IV</td>
<td>NGFI-B</td>
<td>NGF-induced clone B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class V</td>
<td>SP-1/FTZ-F1</td>
<td>Steroidogenic factor 1</td>
<td>Oxysterols</td>
</tr>
<tr>
<td>Class VI</td>
<td>GCNF</td>
<td>Germ cell nuclear factor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class 0</td>
<td>SHP</td>
<td>Small heterodimeric partner</td>
<td>Unknown</td>
</tr>
<tr>
<td>Class 0</td>
<td>DAX-1</td>
<td>Dosage-sensitive sex reversal</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### Steroid receptors
Classification depending on source and type of ligand

<table>
<thead>
<tr>
<th>Ligands:</th>
<th>Endocrine Receptors</th>
<th>Adopted Orphan Receptors</th>
<th>Orphan Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-affinity, hormonal lipids</td>
<td>Low-affinity, dietary lipids</td>
<td>Unknown</td>
</tr>
<tr>
<td>ER α,β</td>
<td>PR</td>
<td>RXR α,β,γ</td>
<td>SF-1</td>
</tr>
<tr>
<td>AR</td>
<td>GR</td>
<td>PPAR α,β,γ</td>
<td>LRH-1</td>
</tr>
<tr>
<td>MR</td>
<td>RAR α,β,γ</td>
<td>LXR α,β</td>
<td>DAX-1</td>
</tr>
<tr>
<td>TR α,β</td>
<td>VDR</td>
<td>FXR</td>
<td>SHP</td>
</tr>
<tr>
<td>EcR</td>
<td>PXR/SXR</td>
<td>CAR</td>
<td>TLX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PNR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NGFI-B α,β,γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ROR α,β,γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ERR α,β,γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RVR α,β,γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GCNF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TR 2,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HNF-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>COUP-TF α,β,γ</td>
</tr>
</tbody>
</table>
Type I: Steroid receptors
1. Sub-family: Steroid hormone receptors

- First TFs (for RNAP-II) cloned: GR and ER

Steroid hormones

- lipids with cholesterol-derived skeleton
- produced in adrenal cortex (ac - binyrebark), gonades (testis/ovaries), placenta
- known receptor ligands:
  - **Aldosterone** = mineralocorticoid with effect on salt metabolism/electrolyte balance [ac]
  - **Cortisol** = glucocorticoid with effect on glucose metabolism [ac]
  - **Testosterone** = androgen (male sex hormone) [testis]
  - **Estradiol** = estrogen (female sex hormone) [ovaries]
  - **Progesterone** [ovaries]
Steroid hormone receptors

- **Characteristic features of steroid receptors (SHR)**
  - binds palindromic HSE (spacer 3 nt)
    - 2x AGAACA - GR, MR, PR, AR
    - 2x AGGTCA - ER
  - binds as homodimers
  - long A/B-domains
  - Found in a chaperone-complex in absence of ligand
    - - ligand: SHR associates with a multicomplex [8-10S] of chaperones (hsp-90,-70, -56) → inactive, no DNA-binding, ligand-receptive conformation
    - + ligand: hsp-complex dissociates → 4S active complex → able to dimerize, bind to DNA, transactivate
  - induced transport to nucleus in specific cases
  - chaperon-function: >inactivation
Steroid hormone receptors

- The relative sizes of the human receptors indicated.
- The numbers above the bars indicate the percentage homology of the consensus regions of the DNA- and ligand-binding domains.
Induced nuclear transport

- Nuclear translocation of GR
  - Time-dependent nuclear translocation of GFP-GR in COS-1 cells in the presence of dexamethasone (DEX).

![Images showing GFP-GR translocation over time](image-url)
Induced nuclear transport - Hsp90?

**Steroid import**
- The steroid released from steroid-binding protein (SBP) is transported into the cytoplasm of the target cell.

**NR-Hsp90 complex**
- When bound to the receptor (R) it induces a conformational change that allows it to bind the Hsp90 dimer, which acts as its chaperone. The NLS of the NR allows the R-Hsp90 complex to translocate into the nucleus.

**In the nucleus**
- Ligand–receptor complex dissociates from Hsp90 and itself dimerizes. The removal of Hsp90 unMASKS the DNA-binding site of the receptor, which allows it to interact with the target gene promoter.

**Not general**
- Many NRs are localized in the target cell nucleus, often tightly bound to chromatin.
Type II: RXR heterodimers
2. Sub-family: RXR heterodimers

- Prototypiske members:
  - RAR [retinoic acid receptor] vitamin A metabolite
  - VDR [vitamin D receptor]
  - TR [thyroid hormone receptor]
  - PPARγ [prostaglandine J2]
  - several “Orphan receptors” with unknown ligand

- Characteristic feature of the RXR-heterodimers
  - Broader chemical variation of ligands
  - Not all ligands are endocrine hormones
  - ligand-independent activation mechanisms exist
  - bind DNA also in absence of ligand
  - bind often to “direct repeats”
  - bind as heterodimers
RXR - a common partner and main regulator

- mediator of receptor heterodimerization → high affinity DNA-binding
- responsive to 9-cis retinoic acid
- three subtypes $\text{RXR}_\alpha, \beta, \gamma$ (+ isoforms $\beta_1 \beta_2$)
  - subtypes - products of individual genes
  - isoforms - products of alternative splicing, alternative promoters etc.
RXR = active or silent partner

- May be a “silent partner” without ligand-binding and response
  - as heterodimer with VDR, TR and RAR
- May be an active partner responsive to 9-cis-retinoic acid
  - e.g. RXR-PPAR responsive to both ligands (synergistic)
Specificity in DNA-binding: the 1-5 rule

- **The 1-5 rule**
  - Direct repeats of AGGTCA with variable spacing (n)
  - DRn where n determines partner
    - DR1 - RXR-RXR
    - DR2 - RXR-RAR
    - DR3 - RXR-VDR
    - DR4 - RXR-TR
    - DR5 - RXR-RAR
  - RXR binds 1. half site, partner binds 2. half site
  - Sequence context modulates
  - Also complex HSEs
### HSEs

- **Hormone response elements**

#### (a) Symmetric sites

- **AGAACA**
- **TGTTC**
- \(n = 3\)
- GR–GR
- PR–PR
- AR–AR
- MR–MR

#### (b) Direct repeats

- **AGGTCA**
- **AGGTCA**
- \(n = 1\)
- RXR
- RAR
- PPAR
- COUP

- \(n = 2\)
- RXR
- PPAR
- RevErb–RevErb

- \(n = 3\)
- RXR
- VDR
- VDR–VDR

- \(n = 4\)
- RXR
- TR
- LXR
- CAR

- \(n = 5\)
- RXR
- RAR
- NGFI-B

#### (c) Monomeric sites

- **xxx-AGGTCA**
- \(xxx = \text{aaa}\)
- NGFI-B
- RevErb
- T/BS
Three DNA-bound dimers with RXR
DBD structure

- Several 3D structures determined
  - without DNA: RXR and RAR DBD (92,93)
  - with DNA: RXR-TR-DR4 (95)
- C4 zinc fingers with major groove contact + 3. helix as a C-terminal extension (CTE) with minor groove contact
- Head-to-tail arrangement $\rightarrow$ dimer interphase different
- DBD alone is a monomer in solution $\rightarrow$ cooperative dimer formation on DRn
- The structural implications of the 1-5 rule
  - n+1 $\rightarrow$ 36° rotation + 3.4 Å translation
  - RXR has to use different interphases for different partners (jfr tannahjul)
Ligand-induced activation
Ligand-binding domain

- **Multiple functions**
  - ligand binding
  - Dimerization interphase
  - hormone-dependent transactivation

- **Solved 3D structures**
  - RXRα LBD without ligand
  - TRα LBD with ligand (see picture)
  - RAR, ER, PPAR, PR, VDR

- **Common fold with 65% α-helices**
  - 12 helices (H1-H12) + a β-turn is arranged as a three-layered antiparallel sandwich, relatively similar in all
**Ligand-binding domain**

- **Activator function (AF-2 or $\tau_c$)**
  - protruding amphipatic helix 12 without ligand (RXR)
  - closed over a ligand pocket with ligand-contact when bound
- **Ligand completely buried in the inner parts of LBDs**
  - Becomes an integrated part of a hydrophobic core
- **Ligand-binding $\rightarrow$ large allosteric changes**
  - From an ”open” apo-form to a compact ”closed” holo-form
Three conformations of LBD

- Ligand-binding ➔ major structural changes
  - From an ”open” apo-form to a compact ”closed” holo-form
- Two distinct conformations for H12 positioned in two conserved hydrophobic grooves - agonist and antagonist grooves on the surface
Ligand-binding domain

- LBDs are signal-responsive regulatory modules adopting distinct conformations as *apo*-receptors, *holo*-agonist bound or *holo*-antagonist bound species.
Ligand-induced conformational change

- Ligand binding first acts through the rearrangement of H3, thus expelling H11, leading to repositioning of H12
LBD conformational change

- Left: the LBD from the crystal structure of the unliganded RXR_α
- Right: the ligand-bound LBD of the RAR_γ.
Model of intact heterodimers

- link DBD with LBD structures
- symmetric LBD + asymm DBD $\rightarrow 180^\circ$ rotation
- Two-step model for binding
  - in solution heterodimers are formed through LBD
  - binds DNA with “swivel” flexibility
  - On proper sites (DRn) the DBDs dimer interphases make contact
Several coactivators and corepressors implicated

Green - Coactivator complexes
Red - corepressor complexes
Coregulators

- **Corepressors** - interact with receptors without ligand

- **SMRT** - "silencing mediator for retinoid and thyroid hormone receptors"
- **N-CoR** - "nuclear receptor corepressor"
- Liberated upon ligand-binding
- C-term: receptor-interaction, N-term: repressor motifs
- Act as an adaptor between NR without ligand and the Sin3-complex with HDAC activity
Coregulators

Coactivators that bind ligand-bound receptors

- several coactivators that stimulate ligand-dependent activation,
- **SRC/p160 family:**
  - SRC-1/NCoA-1 family [steroid receptor coactivator 1 / nuclear receptor coactivator 1]
  - TIF2/GRIP1/NCoA-2 [trx.intermed. factor /glucocort. recept. interact.prot / nuclear receptor coactivator 2]
- CBP/p300 and p/CAF also coactivator for NRs
- Swi/Snf complex
- Probably multi-coactivator complexes
SRC/p160 family

- HAT enzyme and interphase to other complexes

Diagram:
- NR contact
- CBP contact
- HMT contact
- HAT

Domains:
- bHLH
- PAS A/B
- LXXLL/NR boxes
- CBP interaction domain
- CARM1 interaction domain
- Acetyltransferase activity
LxxLL-interactions with coactivators and corepressors

**Coactivators**
- SRC/p160 family
- Associate with NR through LxxLL motif
- Fig: PPARγ LBD bound to a SRC-1 peptide with two LxxLL (yellow)

**Corepressors**
- SMRT and N-CoR
  - C-term: receptor-interaction, N-term: repressor motifs

**Switch**
- absence of ligand allows binding of N-CoR through two LxxxIxxxI/L motifs. Binding of agonist changes LDB-conformation such that a coactivator can be recruited through the LxxLL motif.
Ligand-activation - a switch from an active repressor to a full activator

**Switch**

- hormone binding induces a conformational change in the ligand-binding domain of the receptor, which results in reduced affinity for corepressors and, simultaneously, enhanced affinity for coactivators
Ligand-activation - a switch from an active repressor to a full activator

- Coactivator-link: LxxLL a short helix (green)
- Corepressor-link: longer helix (red)
Involvement of the proteasome in the switch

- Corepressor degradation
  - Recruitment of the ubiquitylation machinery and proteasome-dependent degradation of the repressors are required, at least in the case of the NCoR-containing corepressor complex, to fully promote the release of the corepressors in response to ligand binding.

- NCoEx
  - The nuclear corepressor exchange (NCoEx) factors could represent a further control level.
  - The NCoEx factors TBL1 and TBLR1 are required as adaptors and are components of the NCoR and SMRT corepressor complexes.
Even more complexes - Mediator

Several coactivators for nuclear receptors have been found to be more general than first assumed and are probably identical with or variants of a Mediator-complex

- TRAP - TR-associated proteins
  - Isolated as coactivator for the thyroid receptor (TR)
- DRIP - vit.D receptor-interacting proteins
  - Isolated as coactivator for vitamin-D receptor (VDR)
  - Very similar to TRAP in composition
- ARC - activator-recruited cofactor
  - Isolated as coactivator for SREBP-1a and Sp1
  - Identical with DRIP
- Human Mediator
  - Isolated as E1A-interacting multicomplex with 30 polypeptides that binds the activator-domains of E1A and VP16 (Boyer et al. 1999)
- CRSP, NAT and SMCC
- Comparison reveals many of the same subunits in many of these complexes
Coactivators: both HAT-complexes and Mediator
CARM1 = coactivator associated arginine methyltransferase

- Two-hybrid approach
- CARM1 = H3 specific HMT
Recruitment of two types of activating histone modification enzymes

NR ➔ p160 ➔ acetyl + methylation

Similar recruitment of PRMT1 = H4-specific HMT
Coregulators = targets for signaling $\Rightarrow$ tissue/promoter-specific effects?

- Coregulator function modulated by distinct signaling pathways
- Hypothesis: phosphorylation codes determine the functional specificity of the coregulator for distinct NRs and promoters.
Chain of events

- Ending repression
- Chromatin opening
- Kinase-mediated signaling pathways
- TRAP/DRIP directly contacts basal trx machinery ➔ initiation
- Variability
**Chain of events**

- **Ending repression**
  - Binding of ligand → dissociation of corepressors → recruitment of SWI/SNF remodeling machines

- **Chromatin opening**
  - Binding of SRCs and CBP → local HAT activity and disruption of nucleosomal structure.

- **Kinase-mediated signaling pathways**
  - may communicate directly with NR-regulated promoters. AF-1 phosphorylation might serve to further consolidate ligand-dependent NR-SRC interactions or to recruit SRCs directly to the promoter in the absence of ligand.

- **TRAP/DRIP directly contacts components of the basal trx machinery to effect initiation**
  - certain TAFs may afford some additional input into promoter-specific NR trx.

- **Variability**
  - Local coactivator requirements may vary—for example, a promoter in a readily accessible chromatin context may not require significant chromatin remodeling or HAT activity for assembly of PIC.
Cyclic recruitment and resetting

- The binding of (some) NRs to DNA is characterized by cycles of recruitment and release
  - Experimental evidence ChIP: ERα binding to the pS2 promoter - cycles of 15–20 minutes
  - Coregulators similar cycling - regular resetting of the promoter
  - Experimental evidence photobleaching techniques: GR turnover on synthetic promoters much more rapid exchange, which can be measured in seconds

- Compromise: slow cycles with superimposed rapid "breathing"
Type III: Orphan receptors
3. subfamily: dimeric orphan receptors

- **Definition “orphan receptor”**
  - Based on homology = nuclear receptor
  - Ligand unknown

- **Large family with over 30 subfamilies**
  - Dimeric OR binds both DRn and IR
  - Typically strong constitutive activators/repressors
  - May function independent of ligand

- **Ex 1: hepatocyte nuclear factor 4 (HNF4)**
  - Homodimer
  - Strong constitutive activator

- **Ex 2: COUPs**
  - Dominant repressors
  - Competitive binding + repressor domain + inactive RXR-dimers
  - Function may be to keep target genes turned off in absence of ligand?
The hunt for unknown ligands

- Number of OR > number probable ligands ➔ probably several ligand-independent ORs

- Ex: Nurr1 active without a ligand - its LBD resembles an agonist-bound, trx active LBDs in other NRs
  - Nurr1 LBD contains no cavity as a result of the tight packing
  - Nurr1 lacks a 'classical' binding site for coactivators.

- Those forming RXR-heterodimers are candidates for ligand-dependent NRs
NR and the diet
Bioactive lipids and their nuclear receptors

- Cholesterol, fatty acids, fat-soluble vitamins, and other lipids present in our diets are not only nutritionally important but serve as precursors for ligands that bind to receptors in the nucleus.
Bioactive lipids and their nuclear receptors

<table>
<thead>
<tr>
<th>Nuclear receptor</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoid X receptors*</td>
<td>RXRα,β,γ 9-cis Retinoic acid</td>
</tr>
<tr>
<td>PPARα</td>
<td>Fatty acids, Fibrates</td>
</tr>
<tr>
<td>PPARδ</td>
<td>Fatty acids, Carboprostacyclin</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Fatty acids, Eicosanoids, Thiazolidinediones</td>
</tr>
<tr>
<td>Liver X receptors</td>
<td>LXRα,β</td>
</tr>
<tr>
<td>Farnesoid X receptor</td>
<td>FXR</td>
</tr>
<tr>
<td>Xenobiotic receptors</td>
<td>SXR/PXR, CAR</td>
</tr>
<tr>
<td>Ecdysone receptor</td>
<td>EcR</td>
</tr>
<tr>
<td>Retinoic acid receptors</td>
<td>RARα,β,γ</td>
</tr>
<tr>
<td>Vitamin D receptor</td>
<td>VDR</td>
</tr>
</tbody>
</table>