Nuclear Receptors Superfamily: 
Structural Insights Into Function

Dr. Dino Moras

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48 nuclear receptors in human – many orphans

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Signal transduction pathways and transcriptional regulation

- Growth factors
- Neurotransmitters
- Peptide hormones
- Steroid hormones
- Thyroid hormones
- Adrenal hormones
- PGE

Cross-talk between membrane receptors and nuclear receptors leads to transcriptional regulation through the interaction of transcription factors and nuclear receptors.
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Cofactor binding and transcriptional activation

The modular organization of NHRs

The DNA binding domain (DBD)

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ERα + estradiol (NR3)

11

PR + progesterone (NR3)  AR + testosterone (NR3)

12

RXRα-RARα (NR1)

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NGFI-B (NR4)

X-ray crystallography provides atomic resolution descriptions of the individual modules: DBDs bound to DNA and LBDs.

This picture assembles two of these experimental observations to reconstitute a functional heterodimer.

Multiple alignments

http://bioinfo-igbmc.u-strasbg.fr/Nuclear_Receptors/

- NR LBDs a fragment with C-regions NR sequences: 70% full length LBD sequences + 17 PDGs
- NR LBDs a fragment: 40% available full sequence genomes: 49% full length LBD sequences

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Sequence/structure to function

- Class I (RAR, RXR, PPAR, VDR)
- Class II (USP, RXR/USP)

Homodimers
- Class I
- Class II

Heterodimers

Dimerization and communication pathways in nuclear receptors

- Class I
  - RXR
  - USP
  - VDR
  - LXR
  - ROR

- Class II
  - RXR
  - USP
  - VDR
  - LXR
  - ROR

**Structural Insights Into Function**

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The ligand binding domain (LBD)

Structural basis of some functional properties
- The oligomeric state
- Allosteric control through post-translational modifications, i.e., phosphorylation
- Ligand binding: specificity adaptability (ligand and protein)
- Binding to coactivators, corepressors... the signature motifs
- Ligand dependent (de)activation: agonists and antagonists

Communication pathway in NRs

Allosteric control of hRARα phosphorylation

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Plasticity of the LBD

The mechanism of ligand binding can be best described as a mutual induced fit of ligand and receptor’s LBD

- Two steps are involved:
  - Mutual adaptation through conformational changes and desolvation (dynamical aspect)
  - Stabilisation of the complex in its state of lower energy

The retinoids receptors

RXR

RAR

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Mouse trap model
Large structural modification of the LBD upon ligand binding

Several conformational states of RXR

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Canonical structure of holo-LBD NHRs

Red: signature motif
(F)XXxxxXXxLxxxDQxxLL
conserved hydrophobic core
POD and CBF binding site [XXXL motif]

Yellow: ligand

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Cofactor binding and transcriptional activation

The peptide bears the LXLL signature motif that allows anchoring of the G9A to the dα formed by helices 12 and 18 of the LBD.

The LBD with a bound coactivator peptide (red)

Cofactor binding and transcriptional activation

Ligand binding: specificity, adaptability (ligand and protein)

Binding to coactivators, corepressors... the signature motifs

Ligand dependent (de)activation: agonists and antagonists

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Estrogen receptor-drug interactions

Apo-agonist-antagonist

Structural studies on the ligand-binding domain of the estrogen-related receptor gamma (ERRγ)

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ERR3 ligand binding pocket:
The constitutive state (left) with estradiol docked (right)

Mechanism of ERRγ inactivation by DES

The vitamin D receptor (VDR)
• Crystal structure in complex with 1α,25(OH)2D3
• ‘Superagonists’ conformation
• Structural adaptations to ‘Gemini’

The vitamin D receptor (VDR) Functions
• Calcium and phosphate metabolism
• Maintenance of skeleton architecture
• Anti-proliferative and immunomodulatory activities
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Crystal structure of the VDR LBD

Natural mutations of VDR LBD found in the syndrome of hereditary 1,25-dihydroxyvitamin D-resistant rickets

- Premature stop
- Point mutation

Synthetic vitamin D analogs (20-epi compounds)
- Potential applications in osteoporosis, cancer, autoimmune diseases, ...
- Minimize side effects, hypercalcemia, hyperphosphatemia

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Ligands adapt to the VDR ligand-binding pocket

Crystal structures reveal the presence of water channels

Adaptation of VDR's ligand binding pocket to the 'Gemini' analog

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