

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

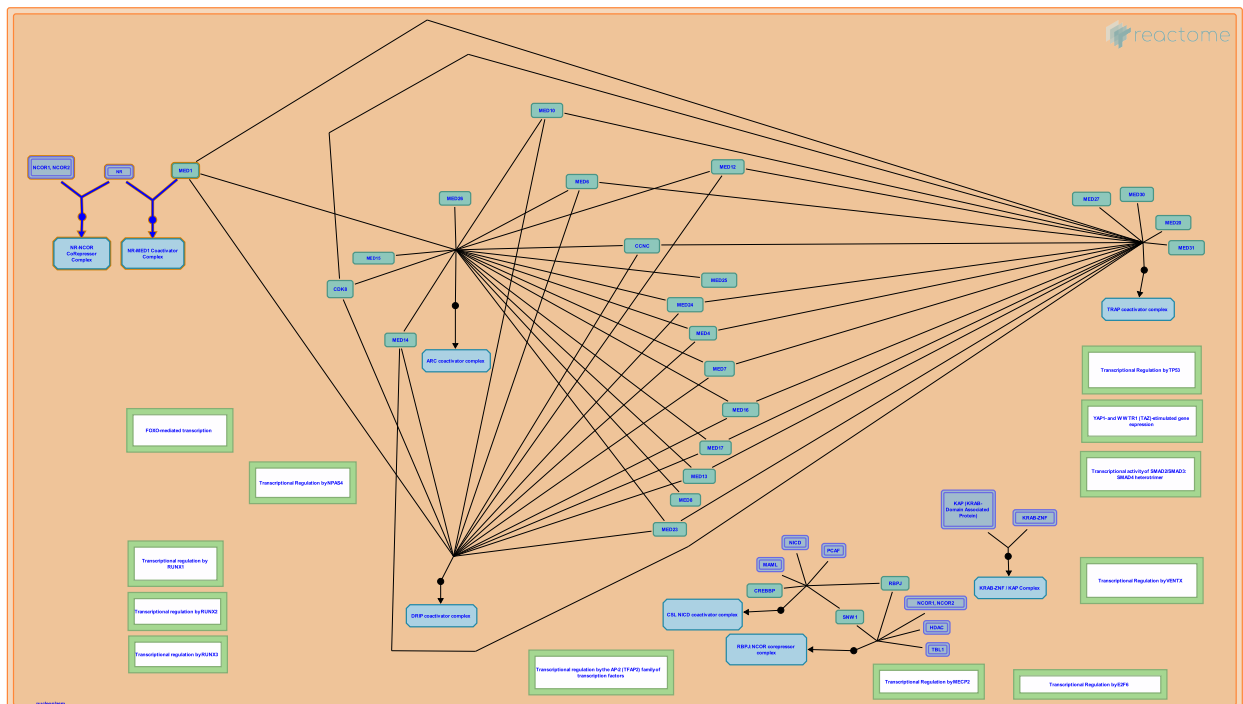
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Reactome database release: 88

This document contains 1 pathway and 2 reactions ([see Table of Contents](#))

Nuclear Receptor transcription pathway ↗

Stable identifier: R-HSA-383280



A classic example of bifunctional transcription factors is the family of Nuclear Receptor (NR) proteins. These are DNA-binding transcription factors that bind certain hormones, vitamins, and other small, diffusible signaling molecules. The non-liganded NRs recruit specific corepressor complexes of the NCOR/SMRT type, to mediate transcriptional repression of the target genes to which they are bound. During signaling, ligand binding to a specific domain the NR proteins induces a conformational change that results in the exchange of the associated CoR complex, and its replacement by a specific coactivator complex of the TRAP / DRIP / Mediator type. These coactivator complexes typically nucleate around a MED1 coactivator protein that is directly bound to the NR transcription factor.

A general feature of the 49 human NR proteins is that in the unliganded state, they each bind directly to an NCOR corepressor protein, either NCOR1 or NCOR2 (NCOR2 was previously named "SMRT"). This NCOR protein nucleates the assembly of additional, specific corepressor proteins, depending on the cell and DNA context. The NR-NCOR interaction is mediated by a specific protein interaction domain (PID) present in the NRs that binds to specific cognate PID(s) present in the NCOR proteins. Thus, the human NRs each take part in an NR-NCOR binding reaction in the absence of binding by their ligand.

A second general feature of the NR proteins is that they each contain an additional, but different PID that mediates specific binding interactions with MED1 proteins. In the ligand-bound state, NRs each take part in an NR-MED1 binding reaction to form an NR-MED1 complex. The bound MED1 then functions to nucleate the assembly of additional specific coactivator proteins, depending on the cell and DNA context, such as what specific target gene promoter they are bound to, and in what cell type.

The formation of specific MED1-containing coactivator complexes on specific NR proteins has been well-characterized for a number of the human NR proteins (see Table 1 in (Bourbon, 2004)). For example, binding of thyroid hormone (TH) to the human TH Receptor (THRA or THRB) was found to result in the recruitment of a specific complex of Thyroid Receptor Associated Proteins - the TRAP coactivator complex - of which the TRAP220 subunit was later identified to be the Mediator 1 (MED1) homologue.

Similarly, binding of Vitamin D to the human Vitamin D3 Receptor was found to result in the recruitment of a specific complex of D Receptor Interacting Proteins - the DRIP coactivator complex, of which the DRIP205 subunit was later identified to be human MED1.

Editions

2008-11-20	Authored	Caudy, M.
2009-05-27	Edited	Caudy, M.
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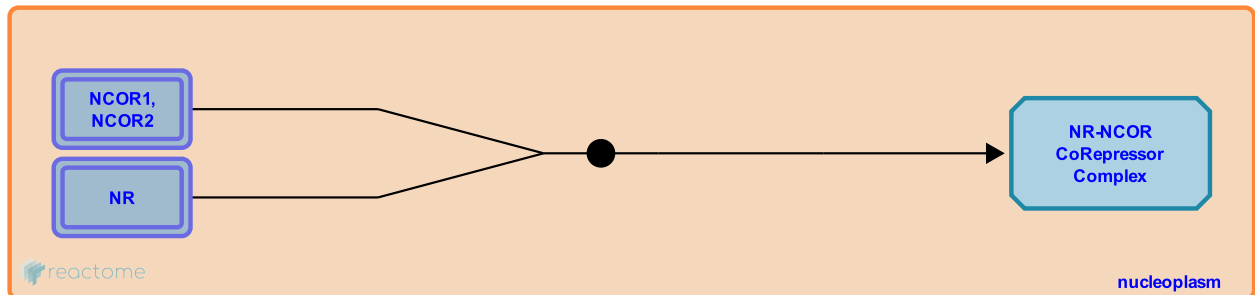
Formation of NR-NCOR Corepressor Complex [↗](#)

Location: [Nuclear Receptor transcription pathway](#)

Stable identifier: R-HSA-382096

Type: binding

Compartments: nucleoplasm



Formation of complex between a single NR protein and an NCOR corepressor protein

Literature references

- Bromleigh, V., Gamble, M., Suldan, Z., Lemon, BD., Freedman, LP., Tempst, P. et al. (1999). Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. *Nature*, 398, 824-8. [↗](#)
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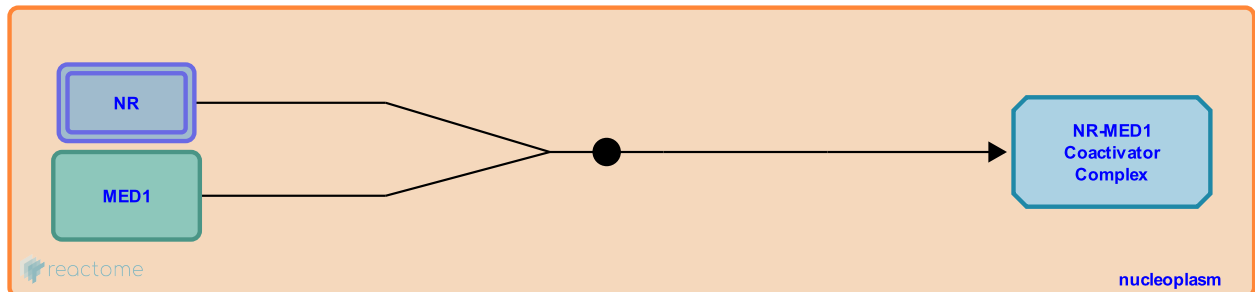
Formation of NR-MED1 Coactivator Complex ↗

Location: Nuclear Receptor transcription pathway

Stable identifier: R-HSA-376419

Type: binding

Compartments: nucleoplasm



THE NUCLEAR RECEPTOR-MED1 REACTION: The Nuclear Receptor (NR) proteins are a highly conserved family of DNA-binding transcription factors that bind certain hormones, vitamins, and other small, diffusible signaling molecules. The non-liganded NRs recruit specific corepressor complexes of the NCOR/SMRT type, to mediate transcriptional repression of the target genes to which they are bound. During signaling, ligand binding to a specific domain in the NR proteins induces a conformational change that results in the exchange of the associated corepressor complex, and its replacement by a specific coactivator complex of either the TRAP/DRIP/Mediator type, or the p160/SRC type. The Mediator coactivator complexes typically nucleate around the MED1 coactivator protein, which is directly bound to the NR transcription factor (reviewed in Freedman, 1999; Malik, 2005).

A general feature of the NR proteins is that they each contain a specific protein interaction domain (PID), or domains, that mediates the specific binding interactions with the MED1 proteins. In the ligand-bound state, NRs each take part in an NR-MED1 binding reaction to form an NR-MED1 complex. The bound MED1 then functions to nucleate the assembly of additional specific coactivator proteins, depending on the cell and DNA context, such as what specific target gene promoter or enhancer they are bound to, and in what cell type.

The formation of specific MED1-containing coactivator complexes on specific NR proteins has been well-characterized for a number of the human NR proteins. For example, binding of Vitamin D to the human Vitamin D3 Receptor was found to result in the recruitment of a specific complex of D Receptor Interacting Proteins - the DRIP coactivator complex (Rachez, 1998). Within the DRIP complex, the DRIP205 subunit was later renamed human "MED1", based on sequence similarities with yeast MED1 (reviewed in Bourbon, 2004).

Similarly, binding of thyroid hormone (TH) to the human TH Receptor (THRA or THRB) was found to result in the recruitment of a specific complex of Thyroid Receptor Associated Proteins - the TRAP coactivator complex (Yuan, 1998). The TRAP220 subunit was later identified to be the Mediator 1 (MED1) homologue (summarized in Bourbon, et al., 2004; Table 1).

The 48 human NR proteins each contain the PID(s) known to mediate interaction with the human MED1 protein. Direct NR-MED1 protein-protein interactions have been shown for a number of the NR proteins. The MED1-interacting PIDs are conserved in all of the human NRs. Therefore, each of the human NRs is known or expected to interact with MED1 in the appropriate cell context, depending on the cell type, the cell state, and the target gene regulatory region involved.

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