

NUCLEAR RECEPTORS

Alternative activation

A detailed study of the orphan receptor Nurr1, a regulator implicated in neurodegenerative diseases, reveals a new way for ligands to control their transcriptional activity.

KRISTEN YOUNG AND SEAN FANNING

Related research article Yu X, Shang J, Kojetin DJ. 2023. Molecular basis of ligand-dependent Nurr1-RXR α activation. *eLife* 12:e85039. doi: [10.7554/eLife.85039](https://doi.org/10.7554/eLife.85039)

Between 10 to 20% of all FDA-approved drugs target a single class of proteins that is critical to human development and physiology across all tissues (Weikum *et al.*, 2018; Dhiman *et al.*, 2018). Known as nuclear receptors, these master regulators can attach to DNA to coordinate transcriptional programs that modify cellular fitness or function (Nettles and Greene, 2005). They are often activated when specific ligands such as metabolites or hormones directly bind onto them at dedicated sites or ‘pockets’ (Olefsky, 2001).

Many nuclear receptors, and in particular many ‘orphan’ nuclear receptors for which an endogenous ligand has yet to be identified, are also involved in disease (de Vera, 2018). Estrogen receptors, for instance, can alter the transcription of thousands of genes in breast cancer cells (Frasor *et al.*, 2003).

Another example is Nurr1, an orphan nuclear receptor critical for the development and maintenance of the neurons that produce dopamine (Zetterström *et al.*, 1997). This receptor has been implicated in dementia, Alzheimer’s and Parkinson’s disease, as well as other neurodegenerative disorders (Jeon *et al.*, 2020; Chu *et al.*, 2002; Decressac *et al.*, 2013). As the expression of Nurr1 diminishes with age, reactivating its production has potential as a therapy against these conditions (Moutinho *et al.*, 2019). Yet

designing small molecules that specifically target Nurr1 has been difficult so far, as the canonical ‘pocket’ which normally welcomes ligands is absent on this receptor (Wang *et al.*, 2003).

An alternative approach may be to target RXR α , a nuclear retinoid receptor which has also been highlighted as a drug target for Alzheimer’s and Parkinson’s diseases. Nurr1 and RXR α bind together to form heterodimers that result in Nurr1 transcriptional activity being repressed (Aarnisalo *et al.*, 2002; Cramer *et al.*, 2012; Friling *et al.*, 2009). In turn, several RXR α ligands and targeted small molecules can modulate the activity of Nurr1, but exactly how this phenomenon takes place remained unclear (Scheepstra *et al.*, 2017). Now, in eLife, Xiaoyu Yu, Jinsai Shang and Douglas Kojetin, who are based at Scripps Research, report using a comprehensive suite of biophysical and structural approaches to reveal how RXR α ligands promote the transcriptional activation of Nurr1 (Yu *et al.*, 2023).

First, the team used reporter gene assays to examine how RXR α as well as various ligands affect Nurr1 transcription in neuronal cells. The experiments showed that the transcriptional activity of the receptor was reduced by the simple presence of the RXR α ligand binding domain; it was also unaffected or slightly decreased while exposed to RXR α antagonists, but enhanced in a graded fashion when the receptor was exposed to ligands which normally activate RXR α or the RXR α -Nurr1 heterodimer.

The classic model of transactivation involves an activating ligand stabilizing certain receptor conformations, which then promotes the recruitment of a repertoire of coregulator proteins that enhance gene expression (Nettles and Greene, 2005). To examine whether this mechanism could

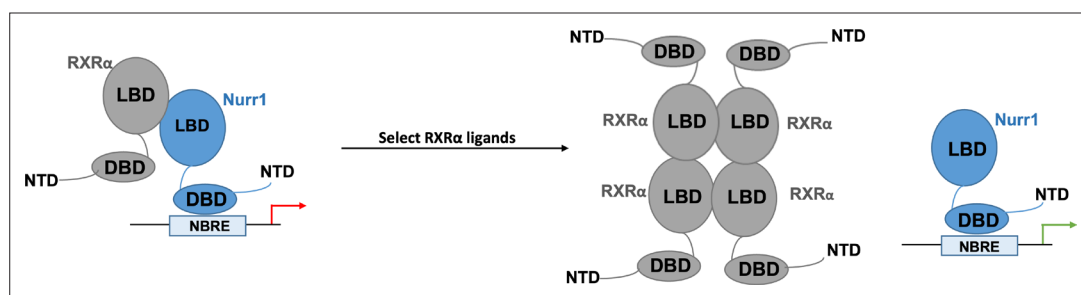


Figure 1. Nurr1 activation may result from selected RXR α ligands disrupting RXR α -Nurr1 heterodimers.

When activated, the orphan nuclear receptor Nurr1 (blue) attaches to DNA response elements (known as NBRE) through its DNA-binding domain (DBD) to promote the transcription of genes that help to regulate the activity of dopaminergic neurons. Previous work has shown that the ligand-binding domain (LBD) of Nurr1 has atypical characteristics which point towards the receptor not being directly activated by ligands. Nurr1 can form heterodimers with another nuclear receptor, RXR α , which reduces its transcriptional activity (red arrow). The work by Yu et al. shows that the binding of certain RXR α agonists leads to the activation of Nurr1. They propose a model by which the ligands destabilise the Nurr1-RXR α heterodimer, leading to four RXR α receptors assembling into a tetramer that prevents reassembly with Nurr1, and Nurr1 existing as a monomer with increased transcriptional activity (green arrow).

explain their results, Yu et al. tracked the molecules using a biochemical FRET assay. However, the experiments showed that Nurr1 transactivation does not in fact correlate with a ligand-induced increase in coactivators binding to RXR α ; this suggests that another, non-classical process is involved instead.

To further investigate how Nurr1 is activated via RXR α ligands, Yu et al. relied on a technique known as isothermal titration calorimetry to precisely dissect the binding dynamics of these various molecules. The experiments revealed that an increase in Nurr1 transactivation is linked to a weakening of the RXR α -Nurr1 heterodimer. More precisely, the analyses show that the formation of the heterodimer releases energy, and is therefore a more stable, favored state; the binding of the ligands onto RXR α , on the other hand, increases the disorder in the system and makes the formation of the heterodimer more difficult.

Next, Yu et al. delved deeper into how exactly Nurr1 becomes activated after the binding of RXR α ligands onto the RXR α -Nurr1 heterodimers. For this, they used nuclear magnetic resonance, which allows them to observe RXR α and Nurr1 in their various configurations. The data revealed that in the presence of the most effective RXR α ligands, Nurr1 shifts from being part of a heterodimer towards existing on its own. The team further interrogated these results by using size-exclusion chromatography, a ‘molecular sieve’ approach which sorts out molecules based on their size. This showed that the RXR α ligands that are the most effective at activating the orphan receptor favored both Nurr1 existing

on its own and four RXR α coming together to form homotetramers. Together, these findings point towards RXR α ligands activating Nurr1 by ejecting it from the heterodimer, and then keeping it on its own by ‘trapping’ RXR α inside oligomers (**Figure 1**).

Taken together, these results reveal an alternative mode of activation for nuclear receptors, one that goes beyond classic regulation mechanisms which require a ligand to occupy the main binding pocket. It is worth noting that the most effective Nurr1 activator was BRF110, an RXR α ligand that has shown therapeutic promise in mouse models of Alzheimer’s and Parkinson’s disease (**Spathis et al., 2017**). Future work should explore the details of this new mechanism, as well as how to harness it to better investigate and ultimately control the transcriptional activity of Nurr1 and other nuclear receptors that form heterodimers with RXR α .

Kristen Young is at the Stritch School of Medicine, Loyola University, Chicago, Maywood, United States
<http://orcid.org/0000-0002-4159-623X>

Sean Fanning is at the Stritch School of Medicine, Loyola University Chicago, Maywood, United States
 sfanning@luc.edu
<http://orcid.org/0000-0002-9428-0060>

Competing interests: The authors declare that no competing interests exist.

Published 12 June 2023

References

Aarnisalo P, Kim CH, Lee JW, Perlmann T. 2002. Defining requirements for heterodimerization between

- the retinoid X receptor and the orphan nuclear receptor Nurr1. *The Journal of Biological Chemistry* **277**:35118–35123. DOI: <https://doi.org/10.1074/jbc.M201707200>, PMID: 12130634
- Chu Y**, Kompoliti K, Cochran EJ, Mufson EJ, Kordower JH. 2002. Age-related decreases in Nurr1 immunoreactivity in the human substantia nigra. *The Journal of Comparative Neurology* **450**:203–214. DOI: <https://doi.org/10.1002/cne.10261>, PMID: 12209851
- Cramer PE**, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, Zinn AE, Casali BT, Restivo JL, Goebel WD, James MJ, Brunden KR, Wilson DA, Landreth GE. 2012. ApoE-directed therapeutics rapidly clear B-amyloid and reverse deficits in AD mouse models. *Science* **335**:1503–1506. DOI: <https://doi.org/10.1126/science.1217697>, PMID: 22323736
- Decressac M**, Volakakis N, Björklund A, Perlmann T. 2013. Nurr1 in Parkinson disease — from pathogenesis to therapeutic potential. *Nature Reviews Neurology* **9**:629–636. DOI: <https://doi.org/10.1038/nrneurol.2013.209>, PMID: 24126627
- de Vera IMS**. 2018. Advances in orphan nuclear receptor pharmacology: a new era in drug discovery. *ACS Pharmacology & Translational Science* **1**:134–137. DOI: <https://doi.org/10.1021/acspsci.8b00029>, PMID: 32219209
- Dhiman VK**, Bolt MJ, White KP. 2018. Nuclear receptors in cancer — uncovering new and evolving roles through genomic analysis. *Nature Reviews Genetics* **19**:160–174. DOI: <https://doi.org/10.1038/nrg.2017.102>, PMID: 29279606
- Frasor J**, Danes JM, Komm B, Chang KCN, Lyttle CR, Katzenellenbogen BS. 2003. Profiling of estrogen up- and down-regulated gene expression in human breast cancer cells: insights into gene networks and pathways underlying estrogenic control of proliferation and cell phenotype. *Endocrinology* **144**:4562–4574. DOI: <https://doi.org/10.1210/en.2003-0567>, PMID: 12959972
- Friling S**, Bergsland M, Kjellander S. 2009. Activation of retinoid X receptor increases dopamine cell survival in models for Parkinson's disease. *BMC Neuroscience* **10**:146. DOI: <https://doi.org/10.1186/1471-2202-10-146>, PMID: 20003337
- Jeon SG**, Yoo A, Chun DW, Hong SB, Chung H, Kim J-I, Moon M. 2020. The critical role of Nurr1 as a mediator and therapeutic target in Alzheimer's disease-related pathogenesis. *Aging and Disease* **11**:705–724. DOI: <https://doi.org/10.14336/AD.2019.0718>, PMID: 32489714
- Moutinho M**, Codocedo JF, Puntambekar SS, Landreth GE. 2019. Nuclear receptors as therapeutic targets for neurodegenerative diseases: lost in translation. *Annual Review of Pharmacology and Toxicology* **59**:237–261. DOI: <https://doi.org/10.1146/annurev-pharmtox-010818-021807>, PMID: 30208281
- Nettles KW**, Greene GL. 2005. Ligand control of coregulator recruitment to nuclear receptors. *Annual Review of Physiology* **67**:309–333. DOI: <https://doi.org/10.1146/annurev.physiol.66.032802.154710>, PMID: 15709961
- Olefsky JM**. 2001. Nuclear receptor minireview series. *Journal of Biological Chemistry* **276**:36863–36864. DOI: <https://doi.org/10.1074/jbc.R100047200>
- Scheepstra M**, Andrei SA, de Vries RMJM, Meijer FA, Ma J-N, Burstein ES, Olsson R, Ottmann C, Milroy L-G, Brunsvelde L. 2017. Ligand dependent switch from RXR Homo- to RXR-Nurr1 heterodimerization. *ACS Chemical Neuroscience* **8**:2065–2077. DOI: <https://doi.org/10.1021/acscchemneuro.7b00216>, PMID: 28691794
- Spathis AD**, Asvos X, Zivara D, Karampelas T, Topouzis S, Cournia Z, Qing X, Alexakos P, Smits LM, Dalla C, Rideout HJ, Schwamborn JC, Tamvakopoulos C, Fokas D, Vassilatis DK. 2017. Nurr1:RXR α heterodimer activation as monotherapy for Parkinson's disease. *PNAS* **114**:3999–4004. DOI: <https://doi.org/10.1073/pnas.1616874114>
- Wang Z**, Benoit G, Liu J, Prasad S, Aarnisalo P, Liu X, Xu H, Walker NPC, Perlmann T. 2003. Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors. *Nature* **423**:555–560. DOI: <https://doi.org/10.1038/nature01645>, PMID: 12774125
- Weikum ER**, Liu X, Ortlund EA. 2018. The nuclear receptor superfamily: a structural perspective. *Protein Science* **27**:1876–1892. DOI: <https://doi.org/10.1002/pro.3496>, PMID: 30109749
- Yu X**, Shang J, Kojetin DJ. 2023. Molecular basis of ligand-dependent Nurr1-RXR α activation. *eLife* **12**:e85039. DOI: <https://doi.org/10.7554/eLife.85039>, PMID: 37102494
- Zetterström RH**, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. 1997. Dopamine neuron agenesis in Nurr1-deficient mice. *Science* **276**:248–250. DOI: <https://doi.org/10.1126/science.276.5310.248>, PMID: 9092472