NRN
Nuclear Receptor News

Welcome to the Retinoid X Receptor (RXR) Issue

The activity of nuclear receptors is affected by multiple protein-protein interactions with one of the most important associations for many NRs being dimerization with retinoid X receptors (RXRs). Three mammalian isotypes exist (RXRα, β and γ), encoded on distinct genes with different tissue distribution, although all RXRs form homo- and hetero-dimers. While there are known ligands for RXR, both endogenous (9-cis retinoic acid) and exogenous (docosahexanoic acid, rexinoids), the purpose of the present article is to introduce RXR as a non-passive player in heterodimeric complex. We hope you find this article of interest, and as always, please visit the Nuclear Receptor Resource (nrresource.org) to find out more information on RXR and other nuclear receptors.

RXR: Hidden, Synergistic, and Phantom Ligands

Receptors for thyroid hormone (TR), retinoic acid (RAR), vitamin D (VDR), peroxisome proliferator-activated receptors (PPARs), and numerous orphan receptors preferentially bind to DNA as heterodimers with a common partner, the retinoid X receptor (RXR) (see Figure 1). In the case of transactivation, RXR serves as an obligate partner and is required for high affinity binding of most RXR partners to their cognate hormone responsive element. However, there are in fact two classes of RXR-dependent heterodimers, permissive heterodimers and nonpermissive heterodimers (Schulman et al., 1997). RXR heterodimers that contain permissive partners (PPARs, LXRs, farnesoid X receptor (FXR)) can be activated by agonists for either RXR or the partner receptor. Importantly, when both partners are activated, they act in an additive or synergistic manner. In contrast, heterodimers formed by RXR and a nonpermissive partner (RAR, VDR) can be activated only by the agonist of the partner receptor. It has been suggested that RXR acts as a silent partner in nonpermissive heterodimers, although as described below, this is not always the case.

When examining the activity of an RXR partner, such as a drug screening project or mechanism of action study, it is also important to account for the ability of this small molecule to affect RXR. For example, tributyl tin (TBT) was initially reported to be a PPARγ agonist and affected genes known to be targets for this receptor. However, it was later shown that TBT was able to activate RXR/PPARγ through binding to RXR and causing a allosteric change that releases transcriptional corepressors (le Maire et al., 2009). Other permissive heterodimers (RXR/PPARδ, RXR/LXR or RXR/NURR1) are also regulated by TBT via binding to RXR (le Maire et al., 2009). Thus, TBT was misclassified as a PPAR agonist, but was a “hidden” RXR ligand. Even in the case of nonpermissive partners, such as RAR, RXR is not truly silent. Remarkably, in the presence of its ligands, RAR “becomes” permissive, and RAR and RXR agonists together have greater effect than the RAR agonist alone (i.e. are “synergistic”) (Germain et al., 2002).

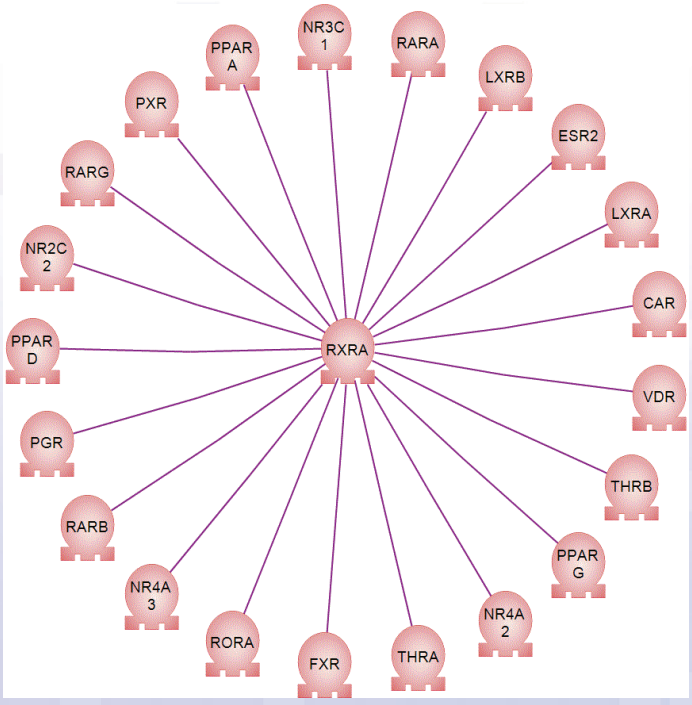

Figure 1. Nuclear Receptors that form heterodimers with RXR

In some instances the binding of a compound to RXR leads to trans-activation mediated by the hormone-dependent activation function (AF-2) of RAR. Thus, even though RAR remains non-liganded, it behaves as if ligand is bound. This unique form of signaling in which ligand binding by one member of the heterodimer leads to activation of transcription by the second non-liganded member of the pair has been termed the “phantom” ligand effect (Schulman et al., 1997). Thus, RXR’s ability to affect multiple nuclear receptor signaling pathways through multiple mechanisms must be considered when examining the activity of its partners.

1 Germain, P., Iyer, J., Zechel, C., and Gronemeyer, H. (2002). Co-regulator recruitment and the mechanism of retinoic acid receptor synergy. Nature 415, 187-192.
2 le Maire, A., Grimaldi, M., Roecklin, D., Dagnino, S., Vivat-Hannah, V., Balaguer, P., and Bourguet, W. (2009). Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. EMBO Rep 10, 367-373.
3 Schulman, I.G., Li, C., Schwabe, J.W., and Evans, R.M. (1997). The phantom ligand effect: allosteric control of transcription by the retinoid X receptor. Genes Dev 11, 299-308.

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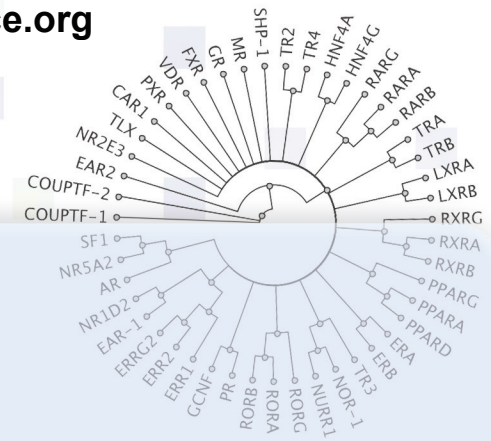

- Welcome to the Retinoid X Receptor (RXR) Issue
- RXRs- Hidden, Synergistic and Phantom Ligands
- New INDIGO RARγ Assay Kit Makes Testing Convenient

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INDIGO Launches New Cell-based RARγ Assay System

A robust, off-the-shelf solution for screening Human Retinoic Acid Receptor Gamma (RARγ) is now available from INDIGO Biosciences, The Nuclear Receptor Company. INDIGO Nuclear Receptor Assay Kits set an unparalleled new standard for convenience and efficacy, going from freezer to data in 24 hours with minimal hands on time. The INDIGO RARγ Assay Systems are the newest offerings from INDIGO's growing line of cell-based, INDIGO Nuclear Receptor Reporter Assay products for on-demand use in drug discovery and development research and toxicology studies. INDIGO Nuclear Receptor Assay Kits enable ultrasensitive detection and quantification of agonist and antagonist activity using stable-glow luciferase chemistry and feature excellent Z' scores and high signal-to-noise ratios. The Company's proprietary cryopreservation process, CryoMite™, enables overnight delivery anywhere in the United States, so researchers can quickly and effectively perform HTS and low throughput screening in 3x 32-, 96- and 384-well plate formats.

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