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**Retinoid X Receptors: common  
heterodimerization partners with distinct functions.**

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## Abstract

Nuclear receptor biology and pathophysiology studies have emphasized the roles of retinoid X receptors (RXRs) in cellular processes ranging from cellular proliferation to lipid metabolism. These pleiotropic effects stem not only from RXR's ability to dimerize with various nuclear receptors, which exert transcriptional control on specific aspects of cellular biology, but also from the permissive nature of some RXR heterodimers, reflecting the ability of RXR ligands to activate this heterodimer. This signaling network is rendered more complex by RXR isotypes (RXR $\alpha$ , RXR $\beta$ , RXR $\gamma$ ) which have some distinctive properties, thereby modulating RXR-containing heterodimer transcriptional activities. This review discusses the emerging roles of RXR isotypes in the RXR signaling network, with possible implications in our understanding of nuclear receptor biology and pharmacology.

## Overview of RXR features

The retinoid X receptors (RXRs) are encoded by three distinct genes located on human chromosomes 9 (RXRA, NR2B1), 6 (RXRB, NR2B2) and 1 (RXRG, NR2B3), or on mouse chromosomes 2, 17 and 1 respectively, and share strong homologies in their coding sequences. RXRs have been initially characterized as heterodimeric partners of the retinoic acid (RARs), thyroid hormone (T3Rs) and vitamin D (VDR) nuclear receptors (NRs) and are required for high affinity binding to DNA of these and other RXR heterodimers<sup>1</sup>. NRs heterodimerizing with RXRs define a subclass which can be activated, or not, through RXR agonism. This (non)permissivity of RXR heterodimers underlines the central and complex roles of RXR in multiple biological processes and also the difficulty for precisely assessing their importance. The realization that RXRs could form homotetramers in solution and bind to DNA as homotetramers and homodimers<sup>2,3</sup> led to the speculation that RXRs may control their own specific signaling pathways, rendering the analysis of the RXR pathway even more complex. Initial genetic analysis of RXR functions essentially pointed to their roles in embryonic development, which is believed to be conveyed mostly through RXR-RARs dimers<sup>4</sup>, and driven by the activation of RARs by the morphogen molecule *all trans* retinoic acid (atRA)<sup>5</sup>. Whereas the biological relevance and functions of atRA are nowadays undisputed, the 9-*cis* retinoic acid isomer, which was initially identified as a bona fide RXR ligand in vitro<sup>1</sup>, has never been

detected in vivo<sup>6</sup>. This prompted the search for novel natural ligands, among which the unsaturated fatty acid docosahexanoic acid (DHA)<sup>7</sup> and  $\alpha$ -apo14'-carotenal<sup>8</sup> activate or repress RXR transcriptional activity respectively. However, these natural molecules are not RXR-specific ligands (rexinoids) and regulate notably the transcriptional activity of peroxisome proliferator-activated receptors (PPARs). The synthesis of rexinoids has revealed their potential as chemotherapeutic agents, exemplified by the successful use of Targretin® (bexarotene) in T-cell lymphoma treatment<sup>9</sup>. However, the promiscuous nature of RXRs has hindered the further development of rexinoids, especially in light of their propensity to cause hypertriglyceridemia<sup>10</sup>, a risk factor of cardiovascular diseases in spite of their beneficial effects on insulin sensitivity and fat mass.

As for all other NRs, the RXR ligand binding domain folds into a three-layered  $\alpha$ -helical sandwich defining a hydrophobic ligand-binding pocket (LBP). In the unliganded state, the AF-2 AD (helix 12) is exposed to the solvent and yields free access of the ligand to the LBP (Figure 1). The RXR LBP is defined by the amino termini of helices 3 and 9, the two beta sheets, helix 8, the H8-H9 loop, and the carboxyl terminus of helix 11<sup>11</sup>. In analogy with RARs, the synthesis of RXR isotype-specific ligands would have been highly desirable. Unfortunately, the strong conservation of LBD and of LBP (ca. 500Å<sup>3</sup>) between RXR isotypes does not allow an easy design of isotype-selective ligands. However, the design of heterodimer-selective rexinoids<sup>12-14</sup> demonstrated that activation of permissive heterodimers through RXR is a viable option for the pharmacological and possibly therapeutical control of dysregulated cellular pathways<sup>15</sup>. Furthermore, the control of RXR heterodimer non-permissivity through the activation of kinase signaling pathways (desubordination) provides another tool to modulate RXR heterodimers transcriptional activity<sup>16</sup>. In this review, we will discuss RXR biology and highlight recent advances in this field to forecast how this increased knowledge may create new options for drug discovery.

### **RXR isotypes: similar but different.**

**Tissue-specific distribution.** The *Rxra*, *Rxrb* and *Rxrg* genes are differently expressed in mouse tissues: *Rxra* is the major isotype in mouse liver, whereas *Rxrb* expression is highest in the central nervous system. *Rxrg* displays a more restricted expression territory, with detectable levels in skeletal muscle and regions of the CNS such as the olfactory bulb and the pituitary glands<sup>17</sup>.

RXRs are expressed as 3 isotypes and numerous isoforms resulting mostly from alternative splicing (Figure 1). The predominant mouse  $RXR\alpha$  isoform is  $RXR\alpha1$ , which encodes a 52kDa receptor. Two additional isoforms have been isolated from adult mouse testis,  $RXR\alpha2$  and  $RXR\alpha3$ , which have a 28 and a 97 amino acid deletion in the N-terminal AF1 domain respectively<sup>18</sup>. Ensembl database inspection also identifies a fourth splice variant  $\alpha4$  potentially generating a 165 aminoacid protein which has not been characterized functionally. Similarly, four mouse  $RXR\beta$  isoforms have been identified. The human homolog of  $mRXR\beta1$ ,  $hRXR\beta2$ , is conserved across species but contains two ATG initiator codons which may produce N-terminal variants<sup>19</sup>. A third isoform, initially termed  $hRXR\beta3$ , contains a SLSR sequence inserted in the ligand-binding domain through the use of an alternative 3'-splice acceptor site, similar to the mouse  $RXR\beta2E$  isoform<sup>20</sup>. This insertion impacts negatively on the ligand binding activity of  $RXR\beta$  and on its transactivation potential. Finally,  $mRXR\gamma1$  is strongly expressed in the brain and muscle, whereas the  $mRXR\gamma2$  isoform has a unique 5'-untranslated region and is expressed highly in both cardiac and skeletal muscles<sup>21</sup>.

The respective role(s) of RXR isotypes and isoforms is not fully understood. Germ line mutations in the *Rxr* genes induce either in utero lethality through congenital heart defects ( $RXR\alpha$ ), or metabolic and behavioral defects [ $RXR\beta$ ,  $RXR\gamma$ , reviewed in<sup>22</sup>]. From a developmental point of view,  $RXR\alpha$  seems to be the main player since mice expressing only  $RXR\alpha$  from one allele are viable, indicating a strong functional redundancy<sup>23</sup>. Tissue-specific inactivation of *Rxra* in hepatocytes<sup>24-28</sup> or epithelia<sup>29,30</sup> induces strong phenotypes, indicating a major role of  $RXR\alpha$  in these tissues, whereas *Rxra* gene knockout has only a mild effect in hematopoietic progenitors<sup>31</sup>. The conditional ablation of  $RXR\alpha$  in adipocytes revealed that this isotype is necessary for adipocyte lipogenesis and hypertrophy, a phenomenon observed in obese animals, but not for adipocyte survival, for which  $RXR\gamma$  can compensate for  $RXR\alpha$  ablation<sup>32</sup>.

**Regulation of RXR expression and cellular localization.** In view of their physiological importance, the mode of regulation of *RXR* gene expression has quite paradoxically received little attention. Only the cloning and characterization of the promoter of the human *RXRA* gene has been reported, revealing a TATA-less sequence with features of housekeeping genes<sup>33</sup>. Direct transcriptional regulation of  $RXR\alpha$ ,  $\beta$  and  $\gamma$  gene expression is seen in severe sepsis and upon LPS

or cytokine treatment in rodent heart and liver<sup>34</sup>. Interestingly, *Rxra*, *Rxrb* and *Rxrg* expression does not follow a rhythmic cycle of expression in metabolically active tissues from C57Bl/6 mice, with the exception of *Rxra* in liver, and in opposition to a number of other RXR dimerization partners such as FXR, PPARs and RARs<sup>35</sup>. Finally, *Rxrg1* expression is down-regulated in pituitary cells by 9-cis-RA through an atypical DR1 response element<sup>36</sup>.

In contrast, a number of reports documented the proteasomal degradation of RXR $\alpha$  in various cellular backgrounds<sup>37</sup>, which appeared to be conditioned by RXR interaction with RAR and the corepressor SMRT<sup>38,39</sup> and increased upon agonist binding<sup>40,41</sup>. Moreover, RXR $\alpha$  breakdown is dependent on MAPK or PKC activity<sup>42,43</sup>, hinting at a link between RXR $\alpha$  phosphorylation and proteasomal-mediated degradation<sup>44</sup>. The sensibility of RXR $\alpha$  to proteasomal degradation is selective, since RXR $\beta$  is resistant to proteasome-mediated degradation in human embryonic kidney (HEK) cells<sup>42</sup>, in mouse 3T3-L1 preadipocytes and in visceral mouse and human adipose tissues<sup>45</sup>. RXR $\alpha$ , but not RXR $\beta$ , is specifically conjugated to ubiquitin both in vitro and in vivo, leading to a marked, specific RXR $\alpha$  breakdown in obese visceral fat. Indeed, mouse and human obese visceral fat overexpress the ubiquitin hydrolase/ligase UCH-L1, which catalyzes, by a yet undefined molecular mechanism, RXR $\alpha$  ubiquitinylation and breakdown<sup>45</sup>. Quite similarly, RXR $\alpha$  is downregulated in many cancer cells and tissues and proteolytically degraded by cathepsin L and/or calpain, generating a cytoplasmic, N-terminally 44 kDa truncated receptor able to interact with the protein kinase Akt and to activate the PI3K/Akt signalling pathway<sup>46</sup>. Interestingly, this 44kDa truncated RXR has also been located in the mitochondrial matrix in which it exerts a transcriptional activity<sup>47,48</sup>, suggesting that RXR can shuttle between the cytoplasmic and nuclear compartments. In line with this, RXR $\alpha$  possess a nuclear localization signal and associates to importin  $\alpha$ , one of the cellular karyophilins binding the nuclear pore complex. When expressed as a GFP fusion protein, RXR $\alpha$  is mostly located in the nucleus but cytoplasmic RXR provides a piggyback transportation to the vitamin D receptor into the nucleus<sup>49,50</sup>. The nucleoplasmic sublocalization to the splicing factor compartment may also be another factor controlling RXR transcriptional activities<sup>51</sup>. LPS treatment of target cells can induce both downregulation of *Rxr* expression and its cytoplasmic relocalization<sup>52</sup>, providing a molecular basis for the observed repression of RXR target genes during TLR4-mediated inflammation. This cytoplasmic relocalization likely depends on RXR $\alpha$  nuclear export signal located in its DBD, which also

conditions the RXR-mediated targeting of Nur77/NR4A1 and of the thyroid hormone receptor to mitochondria to promote apoptosis<sup>53,54</sup>. Thus, in addition to a simple, on-off regulatory mechanism of RXR expression, more subtle mechanisms affecting its cellular localization control RXR transcriptional activities and may generate novel functions for this multi-faceted nuclear receptor. Finally, fine-tuning of RXR transcriptional activity also relies on post-translational modifications (PTM): the MAPK-dependent phosphorylation of human RXR $\alpha$  at serine 260 regulates coactivator recruitment to a RXR-VDR dimer<sup>55</sup> and its degradation through the ubiquitin-proteasome pathway<sup>56</sup>, a PTM which can be controlled through the growth factor status of target cells<sup>57</sup>. In addition, RXR phosphorylation on distinct serine residues is dependant on its association with RAR and can affect the transcriptional cooperation between RAR and RXR {Gianni, Tarrade, et al. 2003 18581 /id}. This non exhaustive list of the role of PTMs on RXR activity suggest a great flexibility of RXR functions according to pathophysiological conditions which affect regulatory signaling pathways.

#### **RXR, a versatile dimerization partner.**

**RXR dimers:** RXRs establish dimeric complexes either spontaneously<sup>58</sup> or in a ligand-dependent manner<sup>59</sup> with a number of other NRs (Figure 2), resulting in distinct functional outcomes. While necessary for high affinity DNA binding of several NRs such as the T3R, vitamin D or RARs, FXR/RXR dimers display a strongly decreased DNA binding upon rexinoid ligation<sup>60</sup>. The DNA binding motifs to which RXR heterodimers bind are, in most cases, direct repeats (DR) containing the AGGTCA heptameric sequence and follow the so called 1 to 5 rule. According to this rule, RXR homodimers and PPAR-RXR heterodimers bind to DR1 motifs, whereas DR2 and DR5 are preferential binding motifs for RXR-RAR heterodimers, and DR3 and DR4 favor the association of vitamin D3 and T3 receptor heterodimers, respectively. This rule is however quite flexible since, for example, FXR-RXR dimers can also bind to inverted repeat (IR) motifs<sup>61</sup> and RXR-RAR dimers to DR4 motifs<sup>62</sup>. It is however clear that the polarization of RXR heterodimers plays a crucial role in the transcriptional outcome upon ligand activation<sup>63</sup>.

RXR dimerization can also confer new biological properties: as mentioned above, RXR association with Nur77/NR4A1 promotes mitochondrial targeting of Nur77 and subsequent apoptosis<sup>64</sup>, whereas RXR association to the PML-RAR $\alpha$  fusion protein unleashes PML-RAR $\alpha$  oncogenic

potential in hematopoietic cells<sup>65,66</sup>. Of note, a number of proteins involved in various biological processes have been shown to interact physically and/or functionally with RXRs (Figure 2), paving the way for the discovery of novel RXR functions. The interaction of RXR with NPAS/MOP4 and Clock, two critical regulators of the circadian feedback loop<sup>67</sup>, suggest for example that circadian rhythms can be brought under the control of endogenous RXR ligands such as DHA, whose availability may depend on the nutritional status. As previously documented, NR-mediated transcription involves DNA double strand breakage and DNA repair<sup>68,69</sup> and in this context, another role of RXR that could also be envisioned is the control of DNA repair through physical interaction with the T:G mismatch-specific thymine-DNA glycosylase (TDG,<sup>70</sup>), in analogy with the reported PCNA-RAR $\alpha$  interaction<sup>71</sup>.

RXRs' ability to homotetramerize or homodimerize has been proposed to be, at least in part, the molecular basis for anticarcinogenic or metabolic properties of rexinoids respectively<sup>2,3</sup>. The dissociation of RXR tetramers has been correlated to the ability of rexinoids to release DNA looping and to trigger apoptosis of breast cancer cells<sup>2</sup>. A PPAR $\alpha$ -independent activation of DR1 response elements has been reported, suggesting that RXR $\alpha$  homodimers may substitute for PPAR $\alpha$ /RXR $\alpha$  on PPAR response elements, and providing a plausible, but not formally proven, molecular basis for the activation of some PPAR $\alpha$  target genes by rexinoids in vivo<sup>3,72</sup>. Taken as a whole, these and other data show that RXRs actively contribute to the transcriptional activity of dimers in which they are incorporated, affecting multiple physiological and pathological processes.

Functional redundancy and the lack of specific RXR isotype-specific ligands hinder a detailed investigation of the specific functions, if any, of each RXR isotype. However, a few reports point to distinct functions for each isotype. We recently demonstrated that RXR $\alpha$ /PPAR $\gamma$  heterodimers were much less sensitive to PPAR $\gamma$  agonism than RXR $\beta$ /PPAR $\gamma$  heterodimers, due to a strong, ligand-insensitive interaction of the SMRT corepressor with RXR $\alpha$ -containing heterodimers<sup>45</sup>. RXR $\beta$  also displays peculiar heterodimerization properties in that it is unable to engage interactions with Nurr1, in contrast to RXR $\alpha$  and RXR $\gamma$ , although the physiological relevance of such heterodimers has not been definitively established<sup>73</sup>. This call for developmental studies of dimerization-deficient Nurr1 mice. Furthermore, the RXR $\alpha$  and RXR $\beta$  subtypes regulate differentially the transcriptional activity of T3R in a chimeric model<sup>74</sup>. In testis, RXR $\beta$  expression is confined to Sertoli cells, indicating a critical



role in spermiation and cholesterol metabolism<sup>75,76</sup>. *Rxrg1* ablation alters the response of cholinergic neurons from the nigrostriatal pathway<sup>77</sup>, in agreement with its expression pattern showing a preferential expression in the brain and skeletal muscle. RXR $\gamma$ -deficient mice display high metabolic rates and resistance to weight gain when fed a high fat diet, which may stem either from an interference with the thyrotrope axis and/or skeletal muscle-specific effects<sup>78</sup>. These data show that RXR isotypes are involved in a plethora of biological responses which are tissue- and very likely isoform-specific. A more thorough investigation using conditional, tissue-specific KO mice would undoubtedly bring new insights into this complex RXR biology.

### **RXR permissivity and metabolic regulations**

Although highly dependent on the model system used to assess this property, RXR-containing heterodimers can be categorized, quite schematically, as either “permissive” or “non-permissive”, as they can be activated, or not, through the RXR moiety. Nuclear receptors with a high affinity for their cognate ligands are mostly found in the non-permissive category, such as RARs, T3R and VDR<sup>79</sup>. These receptors have a noticeable intrinsic repressive activity in the unliganded state. In contrast, low affinity-binding, lipid-activated nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), the bile acid/farnesoid receptor (FXR) or oxysterol receptors (LXRs) are considered as permissive entities, suggesting that the functional control of RXR partners evolved to couple differentially endocrine and metabolic regulations<sup>80</sup>. The mechanism by which this molecular crosstalk takes place is still poorly defined, and is very certainly specific for each heterodimer: indeed, while the C-terminal activating function 2 (AF2, required for coactivator recruitment) of RXR is dispensable for PPAR $\gamma$  synergistic activation, it is required for PPAR $\alpha$  and T3R activation<sup>81,82</sup>. The exact physical basis for this functional synergy is unknown, however, mutagenesis studies and structural studies suggest that one coactivator molecule is recruited per heterodimer, with a single LXXLL motif being anchored to each partner<sup>83</sup>. Intriguingly enough, the structural studies dismissed the possibility of allosteric phenomenons between heterodimeric partners, at least for RAR-RXR heterodimers<sup>84</sup>. In contrast, mutagenesis studies of the RXR-LXR complex spoke in favor of allosteric interactions between the two components of the dimer<sup>85</sup>, a difference which could explain the permissive nature of the LXR-RXR dimer. Importantly, the activation of a given permissive

heterodimer through RXR does not equate activation through the RXR partner: the transcriptional response elicited through RXR overlaps only partially with that elicited through its partner<sup>86-88</sup>. In a detailed study, it was found that activation of LXR target genes in liver by a rexinoid was restricted to genes involved in lipogenesis, whereas those involved in cholesterol homeostasis were left unaffected. While providing a molecular explanation for the hypertriglyceridemic effect of bexarotene and possibly other rexinoids, these data raise the yet unresolved question of whether this reflects a selective permissivity of RXR-LXR heterodimer or another mechanism<sup>89</sup>. This may relate to the differential affinity of LXR and RXR for LXXLL-containing peptides<sup>90</sup> and thus to the assembly of distinct coactivator complexes on each receptor monomer. Alternatively, selective post-translational modifications may control RXR permissivity in a promoter-specific context, in analogy to the protein kinase A-dependent desubordination of RXR in the RXR-RAR heterodimer<sup>16</sup>.

### **Towards heterodimer-specific rexinoids**

RXRs can bind a variety of natural and synthetic derivatives, ranging from  $\omega$ -3 unsaturated fatty acids, the non steroidal anti-inflammatory drug sulindac to organotins<sup>46,91</sup>. A number of RXR agonists with no isotype selectivity have been synthesized, and much like for other NRs, the concept of selective nuclear receptor modulator (SNuRM) applies to this class of compounds. Indeed, the structural diversity of rexinoids translates into distinct patterns of gene expression induced upon treatment of target cells by these molecules<sup>92</sup>, as described previously for other NRs<sup>93</sup>. For example, the two rexinoids HX630 and LG268 induce only partially overlapping gene expression profiles when used in combination with a RAR agonist, Am580<sup>88</sup>. Furthermore, LG268 is a rather promiscuous rexinoid, since able to activate both RXR-LXR and RXR-PPAR $\gamma$  dimers, whereas HX630 induces a preferential activation of RXR-PPAR $\gamma$  dimers<sup>94</sup>. Along the same line, the poorly active rexinoid HX600 acts as an efficient activator of RXR $\alpha$ - and RXR $\gamma$ -Nur77/NR4A1 dimers, but not of RXR $\beta$ -Nur77 dimers, the latter feature being in line with the reported inability of RXR $\beta$  to dimerize with Nur1/NR4A2<sup>95</sup>. Interestingly, the rexinoid LG101506 activates selectively RXR-PPAR $\gamma$  heterodimers, but not RXR-RAR or RXR-LXR heterodimers<sup>15</sup>. In agreement with the predicted biological consequences of PPAR $\gamma$  activation, this compound lowered significantly blood glucose levels in genetically diabetic mice and did not increase blood triglyceride levels in Sprague-Dawley rats

after a seven day treatment<sup>96</sup>. However, RXR antagonism in the RXR-PPAR $\gamma$  dimer has also proven to be efficient in normalizing glycemia and fat mass in animal models<sup>97</sup>, but this pharmacological option has not been explored further. Taken together, these data suggest that the design of heterodimer-specific rexinoids can be envisioned, although no precise rules have emerged yet for an efficient drug design.

### **The RXR cistrome**

The recent availability of deep sequencing techniques led to the identification of RXR dimer DNA binding sites on a genome-wide scale. A consistent finding was that these potential regulatory sites are very often located at intronic locations at a distance from the transcriptional start site of regulated genes, calling for the re-examination of previous promoter studies which identified functional response elements in the vicinity of promoter regions. Another observation was that a vast majority of these heterodimer binding sites are prebound by RXR and that either ligand treatment or increased expression of the RXR partner lead to the expected heterodimer formation. This suggests a model in which RXR serves as a docking site for multiple nuclear receptors, and that the heterodimer composition will vary according to extra-or intracellular cues activating or repressing RXR and/or its dimerization partner. Furthermore, these data provide a general ground for the widely held assumption that RXR increases the DNA binding affinity of RXR-containing heterodimers<sup>98-100</sup>.

### **Concluding remarks**

Heterodimerization is a general, simple mechanism by which a linear signaling pathway can be converted into a very complex network acting in a cell-specific manner in response to physiological or pathological cues. RXRs act as common heterodimerization partners for a number of other nuclear receptors, and as such are often considered as loosening the specificity of the signaling pathway. As a consequence, their usefulness as drug targets has been dismissed. However, the occurrence of several isotypes, and of multiple isoforms raise the possibility, as demonstrated by some reports described above, that RXR functions may be diverse and mediated through distinct molecular entities. An in-depth understanding of their respective biological functions, as well as the identification of

heterodimer-selective synthetic compounds, will undoubtedly unravel novel aspect of RXR biology and pharmacology.

**Future directions box:**

- Is there specific, endogenous ligands for RXR?
- Can these ligands regulate specific metabolic pathways?
- What are the functions for each RXR isotype?
- Are RXRs only transcriptional regulators?

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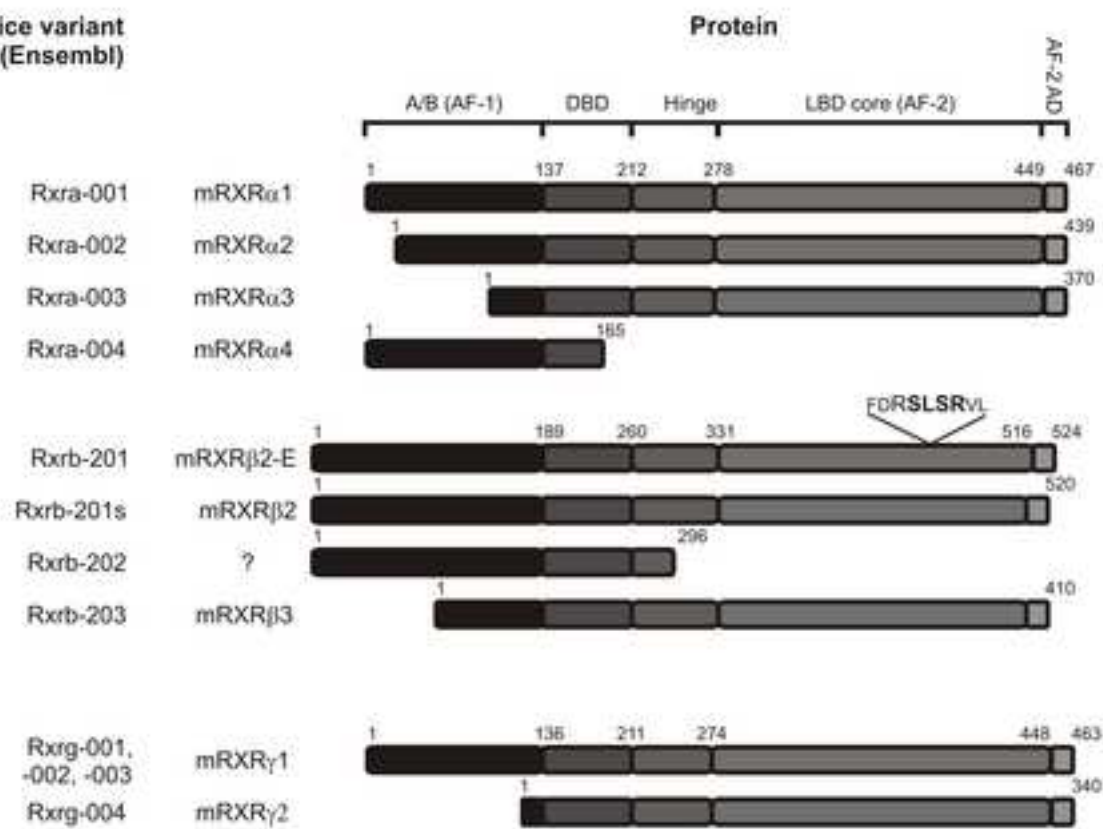
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## FIGURE LEGENDS

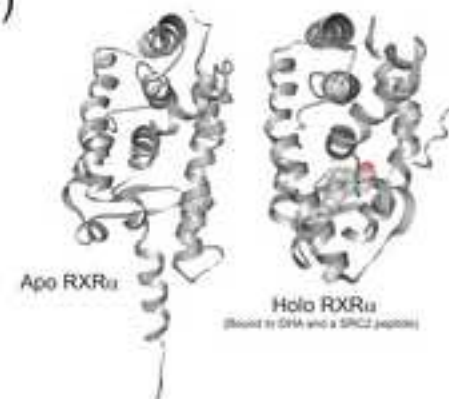
**Figure 1: RXR sequences and structures.** A) RXR primary structure. RXR isoforms have a structural organization similar to that of other nuclear receptors but lack a C-terminal F domain. AF-1: Activation Function-1; DBD: DNA Binding Domain; LBD: Ligand Binding Domain; AF-2: Activating Function 2; AF2-AD: AF2 activation domain (corresponding to helix 12 of the LBD). Splice variant names are indicated on the left, while the structure of the encoded protein is indicated on the right. B) Tertiary structure of the unliganded (Apo-RXR $\alpha$ ) and of the liganded RXR $\alpha$  LBD to docosahexanoic acid (Holo-RXR $\alpha$ ) complexed to a SRC2 peptide. Coordinates were taken from the RCSB protein databank (1LBD and 1MV9) and visualized using the Jmol software. C) Quaternary structure of a full length PPAR $\gamma$ -RXR $\alpha$  heterodimer. Coordinates (3DZY) and molecule structure were obtained as described in B).

**Figure 2: The RXR $\alpha$  interaction network.** Proteins engaging physical and functional interactions with RXR $\alpha$  are indicated and classified according to their main functions. Data were compiled from the visANT database [Hu, Z. et al., 2007, Towards zoomable multidimensional maps of the cell. Nat Biotechnol, 25(5): 547-54] and a PubMed search.

A) Splice variant (Ensembl)



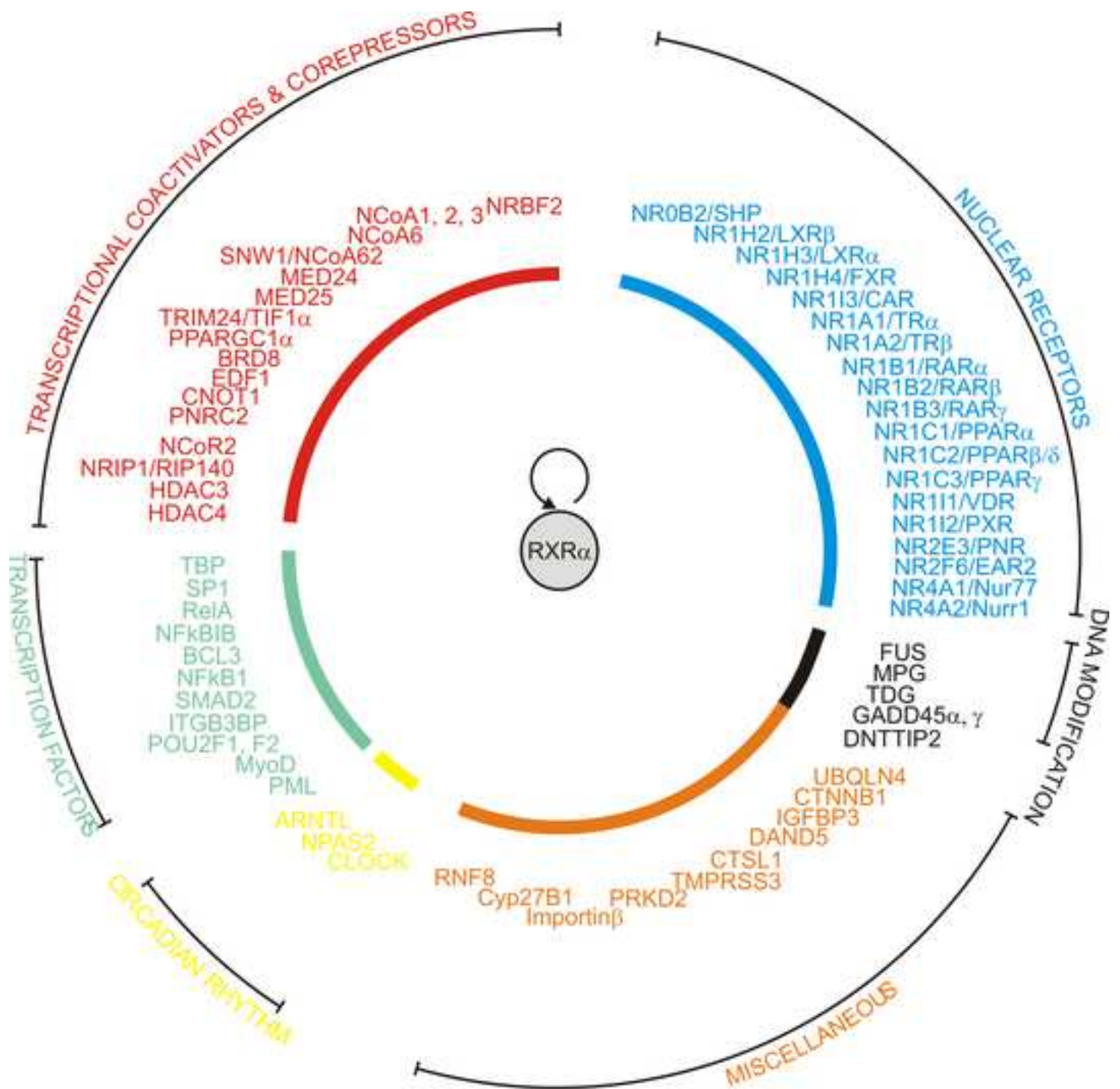
B)



C)



Lefebvre et al., Figure 1



Lefebvre et al., Figure 2