Nuclear Receptor News

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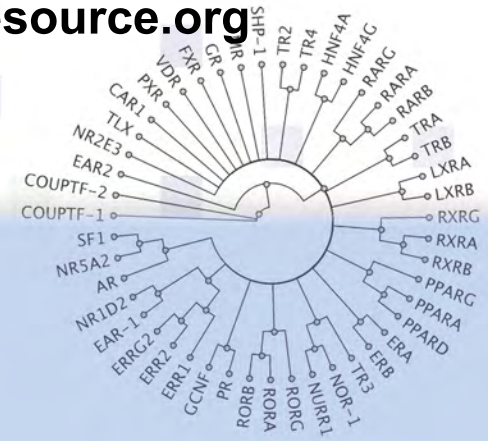

In This Edition

Nuclear Receptor News

Winter 2012 Vol. IV No. 4

Welcome to the "Nuclear Receptor Ortholog " Issue

Orthologs, or orthologous genes, are genes in different species that originated by vertical descent from a single gene of the last common ancestor. Nuclear receptors are specific to metazoans (animals) and are not found in protists, algae, fungi, or plants. There are 270 nuclear receptors in the nematode C. elegans alone while humans, mice, and rats have respectively 48, 49, and 47 nuclear receptors each. Bony fish have a somewhat larger complement of NR genes due to gene duplication, with 68 NR genes. The absence of the sequences encoding Rev-erbβ (NR1D2) and PNR (NR2E3) and the ligand binding domain (LBD) of TLX (NR2E1) in the rat genome and the DNA binding domain (DBD) of LXRβ (NR1H2) in the mouse genome can be explained by gaps in these two assemblies at the expected syntenic locations. Not surprisingly, previous studies utilizing two-species comparisons between human, mouse, and rat or humans, chimpanzee, and mouse genomes revealed that the NR genes are, in general, highly conserved and subject to negative selection, with only a few possible exceptions such as the LBDs of PXR and CAR.

Why does this matter?

Simply put, it matters if you have data suggesting activation of a nuclear receptor in common laboratory animals (rats, mice, fish) and you want to extrapolate this information to humans. This is particularly important if you are studying xenobiotic-sensing NRs such as CAR and PXR, but also when comparing efficacy and potency of ligands for other members of this family.

For more information, please visit the Nuclear Receptor Resource at http://nrresource.org

NRN Nuclear Receptor News

Orthologs

Structure, Relation, and Relevance of Nuclear Receptor Orthologs

NRs share a modular domain structure, which includes, from N-terminus to C-terminus, a modulatory A/B domain, the DNA-binding domain (DBD; C domain), the hinge D domain, the ligand-binding domain (LBD; E domain) and a variable C-terminal F domain that is absent in some NRs [1]. The genes in the NR superfamily generally show nucleotide variation across species consistent with strong purifying selection, particularly in the DBDs [2]. The genomic comparison of the NR families from three related mammals (humans, rats, mice) affords new insight and raises new questions about the structure, function, and evolution of this important family of transcription factors [3]. The LBDs of most NR members have changed little since the divergence of humans and rodents. This is manifested in a phylogenic tree with short terminal branch lengths (see Figure 1). However, three groups, NR1I2-3 (PXR and CAR), NR1H5 (FXRβ), and NR0B1-2 (DAX1, SHP), are significantly more divergent among the three species [3]. In the NR1I group, PXR and CAR share some ligands and regulate overlapping but distinct sets of genes involved in xenobiotic detoxification. Given the central role of CAR and PXR in the xenobiotic metabolism, these two NRs may have evolved faster in response to different sets of environmental challenges encountered by humans, mice, and rats. The rodent PXRs show extensive amino acid sequence divergence at residues that interact with ligands of the human PXR [2]; this manifests itself as distinct ligand preference with existence of species-specific activation by CTZ (see Figure 1). Similarly, the LBD of CAR varies among species at key sites in the binding pocket and it too exhibits dramatic ortholog-dependent activation. The ligand binding pockets of most NRs are higher conserved in receptors that have evolved to respond to endogenous compounds. For example, the LBD of the PPARs are very similar among rat, mouse and humans. Typically this results in similar ligands that may vary slightly in efficacy and potency when comparing orthologs (as shown with the PPARα ligand Wy14,643 in Figure 1). Taken together, this suggests comparing NR orthologs is important for extrapolating between common laboratory species and humans, especially but not exclusively in the case of the xenobiotic sensing receptors CAR and PXR. To learn more about nuclear receptor biology and orthologs please visit the nuclear receptor resource (http://nrresoure.org).

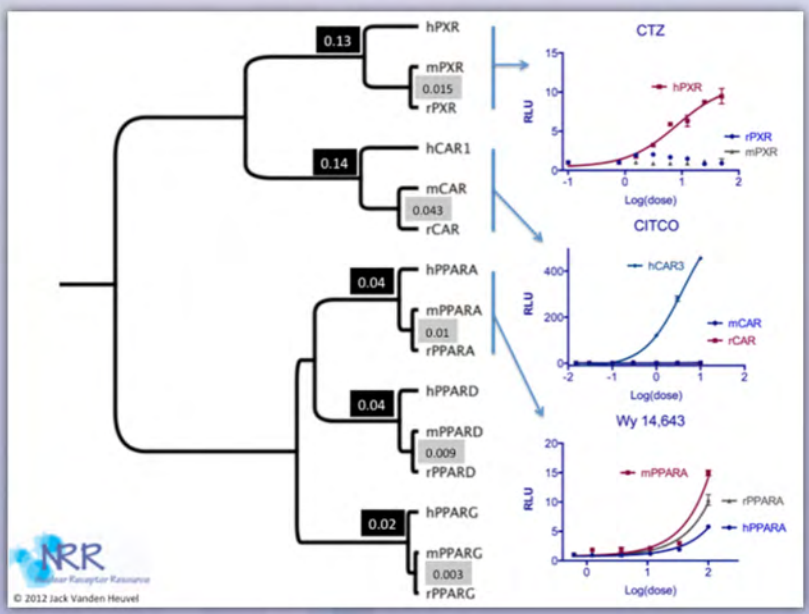

Figure 1. Comparison of PXR, CAR and PPAR orthologs. Numbers in the boxes represent the number of residue changes relative to a common ancestor

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[3]. Zhang Z, Burch PE, Cooney AJ, Lanz RB, Pereira FA, Wu J, Gibbs RA, Weinstock G, Wheeler DA. Genomic analysis of the nuclear receptor family: new insights into structure, regulation, and evolution from the rat genome. Genome Res. 2004
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