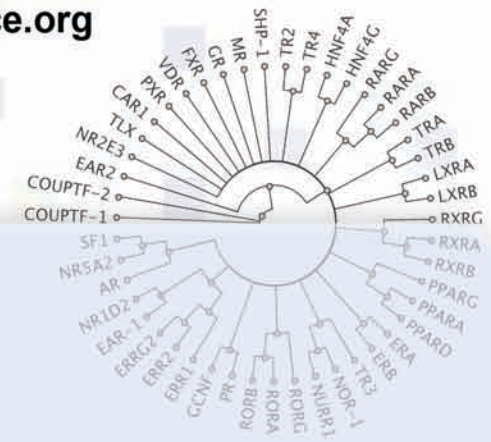
NRN Nuclear Receptor News

Nuclear Receptor News

Dedicated to Nuclear Receptor Research and Researchers

Call for Contributors. info@NRResource.org

Visit us online at NRResource.org



In This Edition

NRN Nuclear Receptor News

Sponsored By: INDIGO Biosciences, Inc. The Nuclear Receptor Company™

Winter 2009 Vol. I No. 2

INDIGO Launches More Cell-based Assay Systems: FXR, PPARα, PPARδ, and LXRα Now Available

Researchers seeking an off-the-shelf solution for screening of activity against human Peroxisome proliferator-activated receptor alpha or delta (also known as beta), Farnesoid X Receptor, or Liver X receptor alpha, now have complete assay systems that are **Ready to Use When You're Ready to Test.** INDIGO Biosciences introduces the human PPARα, PPARδ, FXR and LXRα Assay Systems, the newest additions to our expanding portfolio of cell-based, nuclear receptor reporter assay products for on-demand use in drug discovery and development. INDIGO Biosciences' assays enable sensitive screening of test compounds for agonist or antagonist activities for use in primary screening or secondary and toxicology screening. The all-inclusive assay systems feature high signal-to-noise ratios, and excellent Z' scores. The Company's proprietary cryopreservation process, **CryoMite**™, permits overnight delivery for on-demand use. Kits are optimally configured for HTS or low throughput screening in 3x 32-, 96- and 384-well plate formats.

INDIGO Biosciences, 814-234-1919, www.indigobiosciences.com

NRN
Nuclear Receptor News

NRResource.org – A great resource for researchers

Visit NRResource.org today to see the new and improved site. We have added new articles, drawings, and pathways. The drawings can be used to add graphics to your slideshows or papers. There is also a Blog for discussions of new articles and research in the nuclear receptor field. We are also seeking contributors to help make the site and the newsletter a good resource. Please visit today, and offer any feedback to info@nrresource.org You can also sign up to get this newsletter via email!

Farnesoid X Receptor (FXR, NR1H4)

FXR is a nuclear receptor that has gained a great deal of interest in terms of its biological role and potential as therapeutic target. For more information, the interested reader is directed toward several review articles about this nuclear receptor (for example, (1-5))

The FXR gene and mechanism of action.

FXR was first identified in 1995 from the rat and mouse and later mapped to human chromosome 12q23.1. In rodents, another member of this subfamily of nuclear receptors exists, known as FXR-β (NR1H5), but is a pseudogene in humans (NR1H5P). Conjugated and unconjugated bile acids are the natural ligands that activate FXR-α, with CDCA and its conjugated forms being the most potent natural agonists with an EC_{50} ranging from 4-20 μM. By contrast, mouse FXR-β is activated by lanosterol, an intermediate of cholesterol biosynthesis, illustrating some of the differences that exist in cholesterol metabolism between rodents and humans. We will refer to human FXRα simply as FXR in the subsequent discussion. Several isoforms of FXR are generated as a result of different promoter usage and alternative splicing in humans. These isoforms (FXR-α1, FXR-α2, FXR-α3 and FXR-α4) differ in their tissue distribution and their capacity to activate gene expression in vitro. FXR is mainly expressed in the liver, the gut, the kidney and the adrenal cortex. X-ray crystallography has shown that there are differences in how FXR interacts with steroids and with coactivator peptides. FXR interacts with an inverted repeat spaced with one base-pair response element in the promoter region of its target genes. It is worth noting that FXR is not the only bile-acid-activated nuclear receptor and that pregnane X receptor (PXR, NR1I2) and vitamin D receptor (VDR; also known as NR1I1) share this ability. Consistent with its expression profile in the liver and intestine, FXR regulates enterohepatic recycling of bile acids and thefeed-back regulation of bile-acid biosynthesis and protects against accumulation of bile acids. Activation of FXR in the liver leads to increased conjugation of bile acids followed by the excretion of bile acids from the hepatocyte into the bile canaliculi. In the intestine, FXR induces the expression of the short heterodimer partner (SHP; also known as NR0B2), an atypical nuclear receptor that does not bind to DNA but inhibits the activity of several other nuclear receptors. A summary of the mechanism of action of FXR is shown in Figure 1 and can be found at http://nrresource.org.

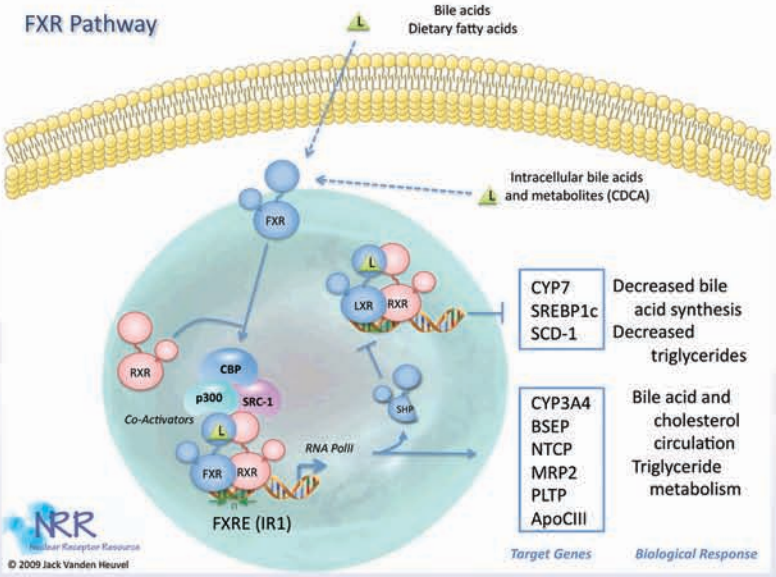


Figure 1. Basic mechanism of action of FXR. See text for details

FXR as a Therapeutic Target

As mentioned above, activating FXR increases transcription of genes that are geared toward preventing synthesis and uptake and promoting excretion of bile acids. One effect of FXR activation is decreased expression of *Cyp7A1* and thus bile acid synthesis; this is accomplished through induction of SHP (short heterodimer partner) which then represses *Cyp7A1* transcription (see Figure 1). FXR has significant effects on lipoprotein metabolism as well, in particular it has the effect of reducing triglycerides. Chenodeoxycholic acid (CDCA) is a bile acid and natural FXR agonist. In animal models, when CDCA or the synthetic ligand GW4064 is administered, they significantly reduce triglycerides and very-low-density (VLDL) cholesterol due to a reduction in the rate of VLDL production and reduce blood glucose. At least some of the mechanisms involved in the reduction of triglycerides include decreased SREBP-1c. Thus an FXR agonist might be expected to be an effective triglyceride-lowering agent, with potentially beneficial effects on glucose metabolism as well.

References

1. Francis, G. A., Fayard, E., Picard, F., and Auwerx, J. (2003) Nuclear receptors and the control of metabolism, **Annu Rev Physiol 65**, 261-311.
2. Modica, S., Bellafante, E., and Moschetta, A. (2009) Master regulation of bile acid and xenobiotic metabolism via the FXR, PXR and CAR trio, **Front Biosci 14**, 4719-4745.
3. Thomas, C., Pellicciari, R., Pruzanski, M., Auwerx, J., and Schoonjans, K. (2008) Targeting bile-acid signalling for metabolic diseases, **Nat Rev Drug Discov 7**, 678-693.
4. Chawla, A., Repa, J. J., Evans, R. M., and Mangelsdorf, D. J. (2001) Nuclear receptors and lipid physiology: opening the X-files, **Science 294**, 1866-1870.
5. Rader, D. J. (2007) Liver X receptor and farnesoid X receptor as therapeutic targets, **Am J Cardiol 100**, n15-n19.