The nuclear receptor superfamily

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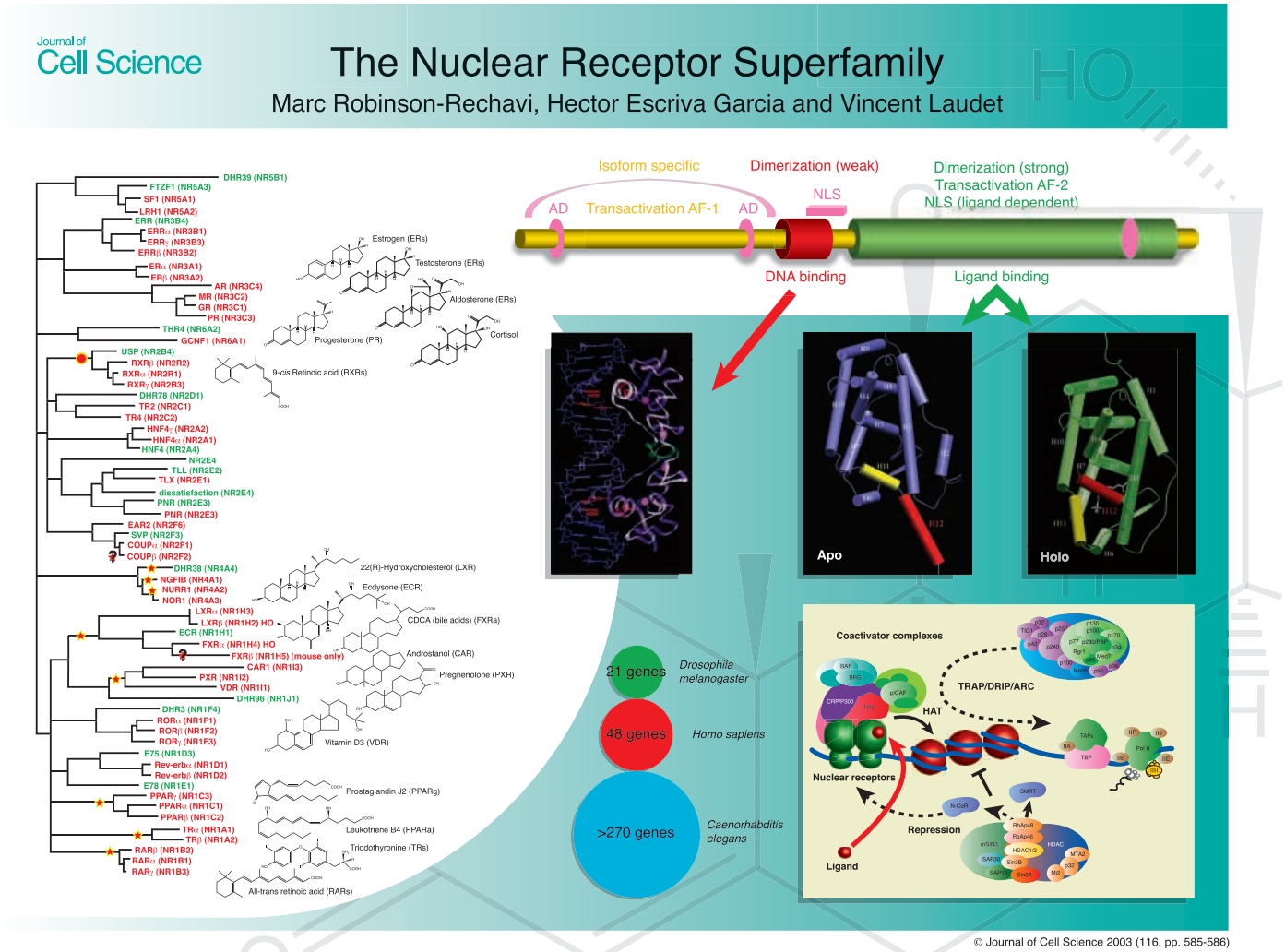
Nuclear receptors are one of the most abundant classes of transcriptional regulators in animals (metazoans). They regulate diverse functions, such as homeostasis, reproduction, development and metabolism (for a review, see Laudet and Gronemeyer, 2002). Nuclear hormone receptors function as ligand-activated transcription factors, and thus provide a direct link between signaling molecules that control these processes and transcriptional responses. A large number of nuclear receptors have been identified through sequence similarity to known receptors, but have no identified natural ligand, and are referred to as 'nuclear orphan receptors'. As nuclear receptors bind small molecules that can easily be modified by drug design, and control functions associated with major diseases (e.g. cancer, osteoporosis and diabetes), they are promising pharmacological targets. The search for ligands for orphan receptors and the identification of novel signaling pathways has become a very active research field (Gustafsson, 1999; Kliewer et al., 1999).

Canonical structure

Nuclear receptors share a common structural organization. The N-terminal region (A/B domain) is highly variable, and contains at least one constitutionally active transactivation region (AF-1) and several autonomous transactivation domains (AD); A/B domains are variable in length, from less than 50 to more than 500 amino acids, and their 3D structure is not known. The most conserved region is the DNA-binding domain (DBD, C domain), which notably contains the P-box, a short motif responsible for DNA-binding specificity on sequences typically containing the AGGTCA motif, and is involved in dimerization of nuclear receptors. This dimerization includes homodimers as well as heterodimers. The 3D structure of the DBD has been resolved for a number of nuclear receptors and



(See poster insert)

contains two highly conserved zinc-fingers – C-X2-C-X13-C-X2-C and C-X5-C-X9-C-X2-C – the four cysteines of each finger chelating one Zn^{2+} ion. The structure represented shows the DBD of the human glucocorticoid receptor (GR) binding to DNA (Hard et al., 1990). Between the DNA-binding and ligand-binding domains is a less conserved region (D domain) that behaves as a flexible hinge between the C and E domains, and contains the nuclear localization signal (NLS), which may overlap on the C domain. The largest domain is the moderately conserved ligand-binding domain (LBD, E domain), whose secondary structure of 12 α-helixes is better conserved than the primary sequence. The 3D structure has been determined for several nuclear receptors (reviewed by Moras and Gronemeyer, 1998), unliganded (apo) or liganded (holo), allowing much better understanding of the mechanisms involved in ligand binding. We show the LBD of RXRα in apo form (Bourguet et al., 1995) and in holo form with its natural ligand 9-cis retinoic acid (Egea et al., 2000) (figures courtesy of Jean-Marie Wurtz, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, France). The E domain is responsible for many functions, mostly ligand induced, notably the AF-2 transactivation function, a strong dimerization interface, another NLS, and often a repression function. Nuclear receptors may or may not contain a final domain in the C-terminus of the E domain, the F domain, whose sequence is extremely variable and whose structure and function are unknown.

Diversity of nuclear receptors

Nuclear receptors form a superfamily of phylogenetically related proteins, with 21 genes in the complete genome of the fly *Drosophila melanogaster* (Adams et al., 2000), 48 in humans (Robinson-Rechavi et al., 2001) [but one more, FXRβ, in the mouse (Robinson-Rechavi and Laudet, 2003)] and, unexpectedly, more than 270 genes in the nematode worm *Caenorhabditis elegans* (Sluder et al., 1999). This diversity has been organized in a phylogeny-based nomenclature (Nuclear Receptors Nomenclature Committee, 1999) of the form NR*xyz*, where *x* is the sub-family, *y* is the group and *z* the gene. In addition to nuclear receptors that have both DNA-binding and ligand-binding domains, sub-family NR0 contains weird nuclear receptors that lack either of these domains, and are not represented in the phylogenetic tree. They include notably Knirps, KNRL and EGON (NR0A1, 2, 3) in *Drosophila*, and DAX1 and SHP (NR0B1, 2) in vertebrates.

The superfamily includes receptors for hydrophobic molecules such as steroid hormones (e.g. estrogens, glucocorticoids, progesterone, mineralocorticoids, androgens, vitamin D3, ecdysone, oxysterols and bile acids), retinoic acids (all-trans and 9-cis isoforms), thyroid hormones, fatty acids, leukotrienes and prostaglandins (Escriva et al., 2000; Laudet and Gronemeyer, 2002). RXRs (USP in arthropods, indicated by a red dot in the phylogeny) play a central role in dimerization of nuclear receptors , and we have indicated its partners by a red star in the phylogenetic tree (for a review, see Laudet and Gronemeyer, 2002); the stars with a question mark indicate the controversial description of heterodimerization of COUP-TF with RXR, and the lack of information on FXRβ.

Mode of action

Nuclear receptors classically act in three steps (reviewed by Laudet and Gronemeyer, 2002): repression, derepression and transcription activation. Repression is characteristic of the apo-nuclear receptor, which recruits a corepressor complex with histone deacetylase activity (HDAC; represented in the lower half of the bottom-right inset). Derepression occurs following ligand binding, which dissociates this complex and recruits a first coactivator complex, with histone acetyltransferase (HAT) activity, resulting in chromatin decondensation, which is believed to be necessary but not sufficient for activation of the target gene. In the third step, the HAT complex dissociates and a second coactivator complex is assembled (TRAP/DRIP/ARC), which is able to establish contact with the basal transcription machinery, and thus results in transcription activation of the target gene. This is of course a very schematic view, and the precise order of events is still debated. It should also be noted that this mechanism is not general, since some nuclear receptors may act as activators without a ligand, whereas others are unable to interact with the target gene promoter in the absence of ligand (the 'repression' step).

References

Adams, M. D., Celniker, S. E., Holt, R. A., Evans, C. A., Gocayne, J. D., Amanatides, P. G., Scherer, S. E., Li, P. W., Hoskins, R. A., Galle, R. F. et al. (2000). The genome sequence of Drosophila melanogaster. *Science* **287**, 2185-2195.

Bourguet, W., Ruff, M., Chambon, P., Gronemeyer, H. and Moras, D. (1995). Crystal structure of the ligand-binding domain of the human nuclear receptor RXR-α. *Nature* **375**, 377-382.

Egea, P. F., Mitschler, A., Rochel, N., Ruff, M., Chambon, P. and Moras, D. (2000). Crystal structure of the human RXRalpha ligand-binding domain bound to its natural ligand: 9-cis retinoic acid. *EMBO J.* **19**, 2592-2601.

Escriva, H., Delaunay, F. and Laudet, V. (2000). Ligand binding and nuclear receptor evolution. *Bioessays* **22**, 717-727.

Gustafsson, J. A. (1999). Seeking ligands for lonely orphan receptors. *Science* **284**, 1285-1286.

Hard, T., Kellenbach, E., Boelens, R., Maler, B. A., Dahlman, K., Freedman, L. P., Carlstedt-Duke, J., Yamamoto, K. R., Gustafsson, J. A. and Kaptein, R. (1990). Solution structure of the glucocorticoid receptor DNA-binding domain. *Science* **249**, 157-160.

Kliewer, S. A., Lehmann, J. M. and Willson, T. M. (1999). Orphan nuclear receptors: shifting endocrinology into reverse. *Science* **284**, 757-760.

Laudet, V. and Gronemeyer, H. (2002). The nuclear receptors factsbook. London: Academic Press.

Moras, D. and Gronemeyer, H. (1998). The nuclear receptor ligand-binding domain: structure and function. *Curr. Opin. Cell Biol.* **10**, 384-391.

Nuclear Receptors Nomenclature Committee (1999). A unified nomenclature system for the nuclear receptor superfamily. *Cell* **97**, 1-3.

Robinson-Rechavi, M., Carpentier, A.-S., Duffraisse, M. and Laudet, V. (2001). How many nuclear hormone receptors in the human genome? *Trends Genet* **17**, 554-556.

Robinson-Rechavi, M. and Laudet, V. (2003). Bioinformatics of nuclear receptors. *Methods Enzymol.* (in press).

Sluder, A. E., Mathews, S. W., Hough, D., Yin, V. P. and Maina, C. V. (1999). The nuclear receptor superfamily has undergone extensive proliferation and diversification in nematodes. *Genome Research* **9**, 103-120.

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