Field of Medical Science and Pharmaceutical Science

Achievement

Discovery of the nuclear hormone receptor family and its application to drug development

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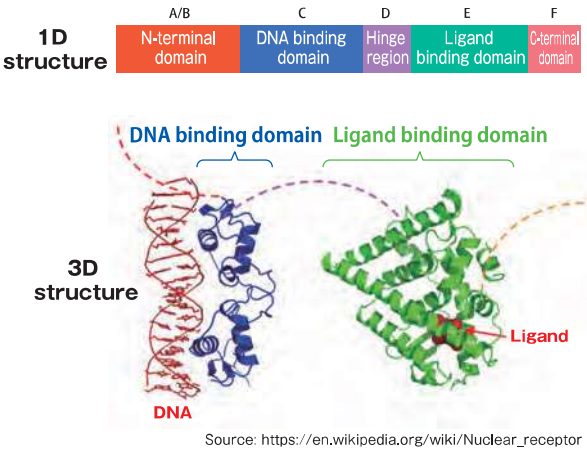
Nuclear receptors that bind fat-soluble hormones and vitamins

The human body maintains homeostasis through the action of various hormones. Hormones are secreted into the blood, and then transported throughout the body to reach the cells of their target organs. The hormones then bind to "receptors" within the cells, and this acts as a trigger to activate the effects associated with those hormones.

Hormones come in two types: water-soluble and fat-soluble. Water-soluble hormone receptors are present in cell membranes, and when a hormone binds with them, the receptors in the cell membrane transmit information into the cell.

Meanwhile, thyroid and other fat-soluble hormones pass through the cell membrane to enter the cell, and can even travel into the nucleus. That is why it was thought that fat-soluble hormone receptors would be present within cells, including inside the nucleus, but those receptors remained unidentified for a long time.

Prof. Ronald Evans was the first researcher in the world to isolate the receptor for the fat-soluble hormone called glucocorticoid, and revealed its structure as a nuclear receptor (Fig. 1).



Source: https://en.wikipedia.org/wiki/Nuclear_receptor

Figure 1: Structural Organization of Nuclear Receptors

Top: Schematic 1D diagram of a nuclear receptor. All nuclear receptors of fat-soluble hormones and vitamins share this basic structure. Bottom: 3D structure of a nuclear receptor.

The functions of the nuclear receptor superfamily

Evans went on to identify a number of new nuclear receptors since isolating the glucocorticoid receptor. He found the receptors for estrogen and thyroid hormones, and also revealed that the receptors for fat-soluble vitamins such as vitamin D and vitamin A are actually nuclear receptors. These led to the understanding that these nuclear receptors are part of a "superfamily" of related molecules with very similar structures and functions.

Nuclear receptors are activated after binding with ligands (hormones, vitamins, and other substances that bind specifically to receptors), and regulate the expression of target genes with specific DNA sequences at the transcription level (Fig.2). Information is transmitted in this way, and this is how hormones and vitamins interact with receptors. In other words, this shows that nuclear receptors act as receptors for fat-soluble hormones, vitamins, and other ligands, and also act as so-called "transcription control factors."

Prior to Evans' work, it was not known that all fat-soluble hormones and vitamins transmit information through a basic shared mechanism. There are 48 types of nuclear receptor within the human body, and his work in clarifying the overall picture surrounding this nuclear receptor superfamily opened the door to new research possibilities in the fields of molecular biology and endocrinology.

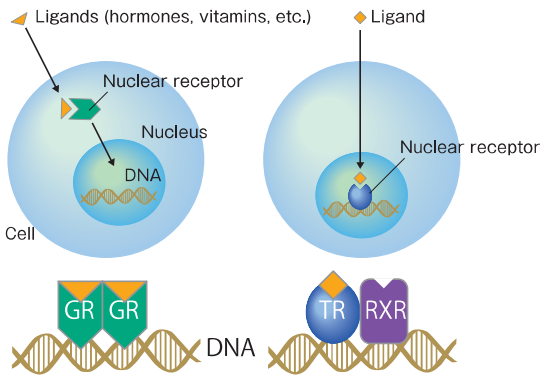


Figure 2: Nuclear receptor function

Nuclear receptors transmit information through one of two mechanisms: through binding with a ligand in the cytoplasm and moving into the nucleus (left), or through binding with a ligand within the nuclear (right). An example of the former is the glucocorticoid receptor (GR), which forms homodimers (a pair of identical molecules bound together) then acts as a transcriptional regulatory factor. An example of the latter is a thyroid hormone receptor (TR), which functions by binding with a retinoid X receptor (RXR) to form a heterodimer (a pair of different molecules bound together). It has also been shown that RXR form dimers with many other nuclear receptors.

Physiological effects and diseases involving nuclear receptors

Members of the nuclear receptor superfamily are present in every tissue in the human body, and they control a variety of physiological activities, including the metabolism, immunity, inflammation, reproduction, bone formation, and cell differentiation and proliferation (Fig. 3). Nuclear receptor functions are associated with a number of diseases, so a number of drugs have been developed to target those nuclear receptors. The United States Food and Drug Administration (FDA) is responsible for approving drugs in the US, and around 15% of the drugs it has approved target nuclear receptors.

For example, clarifying the base of activity mediated by glucocorticoid receptors has led to the development of immunosuppressants and other drugs used to treat various infectious diseases, rheumatoid arthritis, asthma, and more, and these are now being used around the world. In addition, research into vitamin A and vitamin D receptors has revealed the effects of fat-soluble vitamins, which has led to the widespread use of these vitamins in the treatment of leukemia, osteoporosis, psoriasis, and other illnesses.

Opening the door to further drug discovery through an understanding of nuclear receptors

Many members of the nuclear receptor superfamily were referred to as "orphan receptors" when they were first discovered, because the ligands they would bind with were as yet unknown. Evans isolated a number of orphan receptors, including estrogen related receptors (ERR), the retinoid X receptor (RXR), and the peroxisome proliferator-activated receptor γ (PPARγ), and managed to identify some of their associated ligands.

In the case of PPARγ, a nuclear receptor closely associated with adipocyte differentiation and glucose-lipid metabolism, Evans not only identified its endogenous ligands (naturally-occurring ligands present in the body), but he also determined that thiazolidine derivatives used in the treatment of diabetes can act as synthetic ligands for PPARγ.

When controlling transcription, nuclear receptors either activate or suppress transcription by binding to proteins called "transcription coactivators." Evans was also able to successfully isolate transcription coactivators like SMRT, which play an important role in specific organ and tissue functions. This research led to a better understanding of the basis of action and clinical application of selective estrogen receptor modulators (SERM), which are typically used in the treatment of post-menopausal osteoporosis, and of anti-cancer drugs used in treating hormone-responsive cancers (breast cancer, uterine cancer, prostate cancer, etc.)

In these many ways, Prof. Ronald Evans' success in clarifying the overall picture of the nuclear receptor superfamily has not only made an immense contribution to academic research, but also to society as a whole, through his research's impact on drug discovery, clinical medicine, pharmacology, and more.

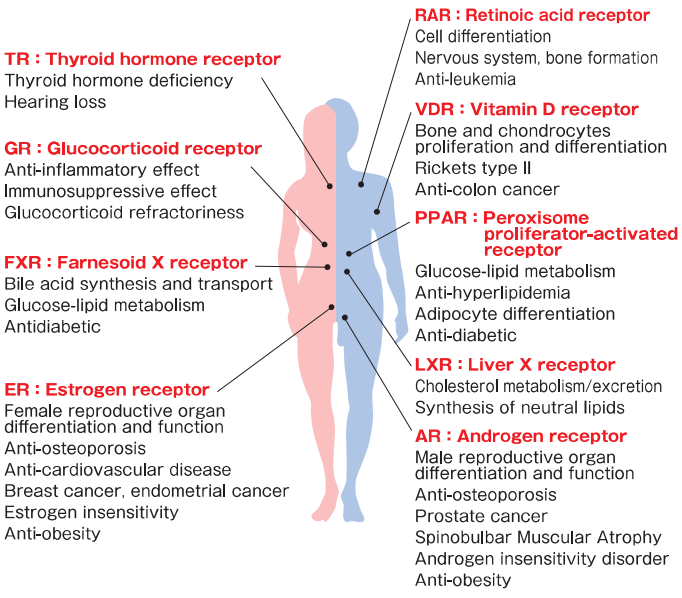


Figure 3: Physiological effects of nuclear receptor superfamily members within the human body, and diseases and therapeutic drugs associated with them.

Table 1: History of the discovery of the nuclear receptor superfamily

Year	Event
1985	First NR cloned (GR)
1986	Cloning of receptor Cloning of thyroid hormone receptor
1987	Cloning of VDR, RAR
1988	Concept of NR superfamily proposed
1990	RXR isolated
1991	Direct repeats revealed to be response elements (3-4-5 rule) Isolation of first PPAR
1992	Identification of first orphan receptor ligand (9-cis RA:RXR) Concept of RXR heterodimer proposed
1995	X-ray structural analysis of RXR-TR heterodimer on direct repeat DNA Cloning of SRC family NR transcription co-factors and N-CoR/SMRT Isolation of LXR, FXR
1996	CBP/p300 revealed to be NR co-activators Discovery that N-CoR/SMRTs bind with HDACs
1998	Isolation of PXR and CAR xenobiotic receptor
1999	1st orphan ligand clinically approved (RXR agonist)
2005	First analysis of NR cistrome
2006	Atlas profiling of NR expression & the Ring of Physiology
2008	X-ray structural analysis of intact receptor on DNA

Re-organized excerpt from Evans, R.M. & Mangelsdorf, D.J. (2014). Nuclear Receptors, RXR, and the Big Bang. Cell 157(1), 255–66.