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MULTI-AUTHOR REVIEW

Nuclear receptors as pharmacological targets, where are we now?

David H. Volle[1,2,3,4]

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Abstract Knowledge of integrative physiology is a major challenge for scientists, as even small deregulation could lead to diseases. Cells communicate with each other to control many processes such as growth, migration, survival, or differentiation. Such interaction could be achieved via several mechanisms either through cell–cell interactions and/or through the signaling of molecules that bind to receptors on the membrane or in the target cells. The produced molecules could have either autocrine, paracrine stimulations, or even act on distant organs (endocrine signaling).

Keywords Nuclear receptors · Therapeutic drugs · Pathophysiology

The nuclear receptor superfamily

Among the receptors, the nuclear receptors (NRs) appear in the last decades to play major roles in both physiology and pathophysiology. The field of research on nuclear receptors has started several decades ago with the identification of the way how hormones impact physiology. Important data regarding structure were already known before the cloning of the first of receptor (glucocorticoids) in 1985 [1]. Since then, numerous studies based on sequence homologies led to the characterization of the nuclear receptor superfamily which now includes 48 members in humans.

Structure

Their structure is subdivided into four functional areas [2].

The N-terminal part (domain A/B) is the most variable in terms of size and protein sequence. It comprises an activation domain, the activating function-1 (AF-1), responsible for the interaction of the receptor with co-activators and co-repressors, regardless of the presence of the ligand. The intervention of these co-factors is essential for the transcriptional activity of the receptors.

The central area (C) is the most preserved in the group, and contains the DNA-binding site (or DBD-, DNA-binding domain). It comprises two zinc finger structures involved on the one hand in the DNA binding and in the other hand in the receptor dimerization. Thus, NRs modulate transcription of their target genes through their binding to specific promoter sequences called hormone response elements (HRE). The HREs are generally composed of two half-sites of six bases each, connected by a spacing of 0–5 bases, and organized in direct repeats (DR, direct repeats), inverted (IR, inverted repeat), or mirrored (ER, everted repeat). Nuclear receptors bind to these response elements in the form of homodimers, heterodimers, or monomers.

The domain D is a flexible hinge region connecting the DBD to the ligand-binding domain (LBD). It would allow the rotation of the LBD to facilitate attachment of the dimer on DR or IR type answers. It also contains the nuclear localization signal (NLS, nuclear localization signal) which ensures the transfer of the receptor in the nucleus.

✉ David H. Volle
david.volle@inserm.fr

[1] INSERM U 1103, Génétique Reproduction et Développement (GReD), Campus Universitaire des Cézeaux, 10 avenue Blaise Pascal, TSA 60026, CS 60026, 63178 Aubière Cedex, France

[2] Université Clermont Auvergne, GReD, 63000 Clermont-Ferrand, France

[3] Université Clermont Auvergne, GReD, 63170 Aubière, France

[4] CNRS, UMR 6293, GReD, 63170 Aubière, France

The domain E contains the LBD which provides the specificity and selectivity of the physiological response. It also contains a second transcription activation domain (AF-2).

Functions

Several classifications of nuclear receptors have been proposed. From a functional point of view, there are three major classes of nuclear receptors: the endocrine receptors with a high affinity ligand, the orphan nuclear receptors "adopted" with low-affinity ligand, and the nuclear orphan receptors.

The endocrine receptors

These receptors respond to steroid hormones as ligands. There are five classes: androgens, estrogens, progestins, glucocorticoid, and mineralocorticoid. In the absence of ligand, these receptors are complexed with HSP (heat-shock protein)-type chaperones that sequester the NRs in the cytoplasm, thus rendering them inactive. Binding of ligand results in the departure of HSPs, the nuclear translocation of the receptor, and its dimerization. The receptors of this class specifically bind as a homodimer on the promoter of target genes to promote expression by recruiting transcriptional co-activators.

Outside of this mode of action called 'genomic', some of these steroid hormone receptors can act by other faster molecular mechanisms called 'non-genomic'.

The adopted receptors

The orphan nuclear receptors "adopted" are, in turn, permanently fixed to their response elements and associated transcriptional co-repressors maintaining chromatin in a non-permissive state for transcription. Ligand binding causes a change in receptor conformation to the release of co-repressors and recruitment of co-activators leading to the activation of the transcription of target genes. These receptors act predominantly as a heterodimer binding with the receptor for 9-cis retinoic acid retinoid X receptor (RXR). However, there is evidence that they are also capable of acting as homodimers or monomers. This class of nuclear receptors includes members, such as LXRα, β (liver X receptor, NR1H3, and NR1H2) and peroxisome proliferator-activated receptor (PPAR and NR1C) involved in the control of lipid metabolism.

The orphan receptors

Orphan receptors are proteins whose structure has a high identity with the other members of the nuclear receptor family, but whose natural ligands have not yet been identified. Among this class of NRs, some of the most studied are the estrogen-related receptors (ERR, NR3B1; 2, or 3), or the steroidogenic factor 1 (SF1; Nr5A1).

NRs in human diseases

NRs play important regulatory roles virtually in all biological processes. Nuclear receptors regulate transcription of target genes involved in various functions, such as development, cell differentiation, reproduction, and general metabolism. In human, the relevance of these signaling pathways is highlighted by the identification of polymorphisms or mutations in the genes-encoding NRs and the association with diseases. In that line, mutation in the gene encoding the bile acid nuclear receptor FXRα (farnesol-X-receptor; Nr1H4) was associated with progressive familial intrahepatic cholestasis [3]. Another example was the identification of mutations for the gene-encoding DAX1 (NR0B1) in patients with hypogonadism [4].

Exogenous modulations

The roles of NRs have been mainly identified in the last decades through the use of transgenic mouse models.

Even though lot of advances have been made in the field, the identification of their physiological ligands still needs to be a priority of scientists in the field, as numerous receptors still need to be de-orphanized. This is important to better understand the roles of the NRs in physiology and diseases. Indeed, it has been nicely demonstrated for several NRs that the activation and inhibition could have either opposite or identical effects on particular molecular mechanisms (gene regulation) and physiological impacts.

Pharmaceutic drugs

In addition to the identification of their ligands, the development of specific synthetic agonists or antagonists has also increased our view of the in vivo activities of these NRs. As the activity of the nuclear receptors can be modulated by ligands, they are important putative targets for drug development, leading pharmaceutical companies to put efforts on this.

As far as the development of therapeutic drugs is concerned, it is also necessary to reinforce research to define the potential secondary impacts of the modulation of NR pathways during long-term treatment, as it could be the case for diseases like diabetes or obesity.

NR, where are we now?

This present issue, focusing on particular members of the superfamily, deals with recent advances in the studies of NRs and their potential interest for different physiological and/or pathological conditions.

Among the NRs, Retinoid pathways through the RAR (retinoic acid receptors, NR1B1/2/3) have been studies for decades, as they are involved in many physiological processes from development up to adulthood. All these studies lead to the use of retinoids as medicine. However, as highlighted by Comptour et al., the identification of the mechanisms of action of RAR is critical, regarding their potential use during pregnancy and thus the potential teratogenic effects induced.

Among pathological conditions, those appearing during aging became sanitary problems, as our society is getting older. In that line, neurodegenerative diseases and bone loss are part of the most frequently diagnosed.

Immunity and inflammatory processes are defense mechanisms in the nervous central system to fight against diseases, such as degenerative ones. It can be triggered by accumulation of misfolded proteins, release of cell membrane components resulting from neuronal damage, blood components that result from blood–brain barrier disruption, or oxidative stress following hypoxia. Several NRs are studied to better understand the development of these diseases. Here, Mouzat and collaborators illustrate this field of research through the recent data in the identification of LXRs as potential actors and therapeutical targets for the treatment of these pathologies.

Considering bone loss, several signaling pathways have been demonstrated to be involved in last decades. Such pathology has been for long associated with hormone status and the signaling of their respective NR as illustrated in postmenopausal women. Here, the review from Zhang illustrates the recently identified actions of the ERRs.

It has been highlighted by numerous studies that these NRs are valuable targets for addressing a range of pathologies, including metabolic syndrome and cancer. In that line, the review from Smith's laboratory deals with the interest of NRs in treatment of skin diseases. It is now clear that NRs act as part of a protein complex leading to transcription of the target genes. The development of therapeutic molecules requires defining the roles of the nuclear receptors and also the involved molecular mechanisms. Indeed, co-factors have been demonstrated to be key in the impact of NRs on physiology and pathophysiological conditions. This is illustrated in the present issue, with the review of Ducheix et al. reporting the main roles of PGC-1β, a nuclear receptor/transcription factor co-activator in the context of non alcoholic fatty liver diseases.

Conclusions

The identification of the involvement of the NRs could be helpful to define new diagnosis and/or prognostic tools in regard to the etiology and/or the progression of the diseases. In addition, they still good candidates for the cure of diseases, and real efforts have been made to generated drugs minimizing potential secondary deleterious effects of long-term treatments. Moreover, the analysis of NRs polymorphism could also be important to propose personalized medicine in the context of particular diseases.

It also appears in the recent years that the NRs are targeted by environmental molecules, such as environmental pollutants. As consequence of these abnormal modulations, the NRs activities are associated with the development of environmental diseases. In that line, NRs offer an important field of research, as they play important regulatory roles virtually in all biological processes. In this context, the characterization of their impacts during utero/neonatal period is a challenge, as such exposures could lead to immediate diseases [5], but also to later ones in adulthood [6] and even transgenerational transmission of abnormalities [7]. In that context, the endocrine receptors have been so far the most studied in line with endocrine disrupters; but it cannot be excluded that other nuclear receptors could be involved.

Even though there is still a long road to go, the different aspects of NR impacts on physiology and/or pathophysiology highlighted by these reviews support the idea that this field of research will continue to fascinate researchers with considerable impacts on clinical approaches on major human health problems, such as developmental abnormalities, metabolic diseases, cancers, and aging disorders.

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