Nuclear Receptor Minireview Series*

The nuclear receptor superfamily describes a related but diverse array of transcription factors, which include nuclear hormone receptors (NHRs)\(^1\) and orphan nuclear receptors. NHRs are receptors for which hormonal ligands have been identified, whereas orphan receptors are so named because their ligands are unknown, at least at the time the receptor is identified. Unlike hormones for cell surface receptors, lipophilic hormones can traverse the plasma membrane to the cell interiors where NHRs transduce signals from surface receptors. NHRs function as homodimers binding to direct repeats of 5'-CGGTCA-3' (Class 3) or as monomers binding to single site REs (Class 4).

All of the nuclear receptors have common structural features (Fig. 1), which include a central DNA binding domain (DBD) responsible for targeting the receptor to highly specific DNA sequences comprising a response element (1). The ligand binding domain (LBD) is contained in the C-terminal half of the receptor and recognizes specific hormonal and nonhormonal ligands directing specificity to the biologic response. These receptors contain variable N-terminal and C-terminal domains, as well as a variable length hinge region between the DBD and LBD. Nuclear receptors can exist as homo- or heterodimers with each partner binding to specific RE sequences that exist as half-sites separated by variable length nucleotide spacers between direct or inverted half-site repeats. Several years ago Manglesdorf et al. (2) proposed four categories of nuclear receptors in which Class 1 receptors include the known steroid hormone receptors, which function as homodimers binding to half-site RE inverted repeats. Class 2 receptors exist as heterodimers with RXR receptor partners and function in a ligand-dependent manner. The second two classes include orphan receptors, which function as homodimers binding to direct RE repeats (Class 3) or as monomers binding to single site REs (Class 4).

Given the widespread relevance of the superfamily of nuclear receptors to almost all aspects of normal human physiology, the role of these receptors in the etiology of many human diseases, and their importance as therapeutic targets for pharmaceuticals, it is obvious that a detailed understanding of these systems has major implications, not only for human biology but also for the understanding and development of new drug treatments. In composing this minireview series, it is quite clear that it is not feasible to comprehensively review any of the separate areas in great detail, and all of the minireviews in this series contain references to more extensive review papers on particular topics. As in all minireviews, the purpose of this series is to highlight major themes and new developments in these areas and to point out common molecular and biochemical principles that broaden our understanding of these complex biological processes.

The first article in the series is entitled “Coregulator Codes of Transcriptional Regulation by Nuclear Receptors” authored by Michael G. Rosenfeld and Christopher K. Glass. This review covers the complex and ever-growing network of interactions between coregulatory proteins and nuclear receptors. These regulatory proteins form multicomponent assemblies with the nuclear receptors, and these complexes can serve as coactivators or corepressors. The specific proteins in these complexes can bind to nuclear receptors via specific amino acid sequence motifs in a ligand-dependent or independent manner and can provide enzymatic or scaffolding functions. These coregulators influence chromatin remodeling by histone acetylation/deacetylation, methylation, and possibly other events. In general, ligand binding to nuclear receptors causes an exchange of coactivators for corepressors to facilitate transcription. This review also points out that the coregulatory proteins themselves are subject to biochemical and functional regulation by various signaling pathways. Far more coregulatory molecules have been identified than can bind to a given nuclear receptor, and given recent findings of rapid turnover of these complexes on DNA, it is possible that they work in a combinatorial or sequential manner to exert transcriptional control. Given the tissue specificity of some coregulators, their ability to be modified by various other signaling molecules, and possible combinatorial functions, one can envision that a given nuclear receptor could exert diverse effects depending on the environmental context of a given tissue, cell, or specific promoter.

The estrogen receptor (ER) is perhaps the most well defined nuclear receptor system from the point of view of biologic responses and clinical implications. “Multifaceted Mechanisms of Estradiol and Estrogen Receptor Signaling” by Julie M. Hall, John F. Crouse, and Kenneth S. Korach reviews the major features of this important nuclear receptor system. There are two subtypes of the ER (ERα and -β), which are products of distinct genes but show differences in tissue expression. Although quite similar in structure, the two ER subtypes display structural differences and can mediate overlapping but different sets of biologic functions. This is best exemplified in the ERβ versus ERα knockout mice, which have quite different phenotypes. However, it is also clear that ERβ can substitute for ERα in some biologic pathways. Furthermore, ERβ can interact with the same ERE as ERα, and the two ER subtypes can also form heterodimers, indicating that in cells that express both ER subtypes, the ratio of the two will effect estrogen action. This review provides a discussion of the classical mechanisms of estrogen action mediated through the ER and EREs, as well as nonclassical mechanisms in which EREs can be modulated by ligand independent means. Genomic actions of ERs can also be exerted in the absence of direct DNA binding by mechanisms in which liganded EREs interact directly with other transcription factors such as Fos and Jun, influencing their function at AP-1 sites. To add to the complexity of ER action, it has now been proposed that estrogens can exert nongenomic effects by binding to plasma membrane receptors that directly mediate biologic responses. Finally, this review provides an incisive discussion of the selective estrogen receptor modifier concept, which holds that different ligands form specific three-dimensional structures with receptors that lead to tissue- and perhaps cell-specific biologic effects. This concept has already had ramifications on the clinical front, where it has been shown that different selective estrogen receptor modifier compounds (the Type 2 anti-estrogen Raloxifene and the Type 3 anti-estrogen, Tamoxifen) exert unique estrogenic effects in a tissue-specific manner. This is an important area of pharmaceutical discovery in which there is hope of developing agents that exert only the beneficial and not the potentially harmful effects of estrogens.

Peroxisome proliferator-activated receptors (PPARs) exert diverse effects on fat and carbohydrate metabolism and are major targets for therapeutic agents in metabolic diseases. This has gen-

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1 The abbreviations used are: NHR, nuclear hormone receptor; DBD, DNA binding domain; LBD, ligand binding domain; ER, estrogen receptor; ERE, estrogen response element; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione.
FIG. 1. Structure/function organization of nuclear receptors. The six domains (A–F) of nuclear receptors comprise regions of conserved function and sequence. All of the nuclear receptors contain a central DBD (region C), which is the most highly conserved domain and includes two zinc finger modules. A LBD (region E) is contained in the C-terminal half of the receptor. Situated between the DBD and LBD is a variable length hinge domain (region F), which is the most highly conserved domain and includes two zinc finger regions. Most receptors also contain a variable length C-terminal region important for dimerization are contained within the DBD and LBD.

The bulk of this paper focuses on the PPAR receptor. This receptor clearly plays a critical role in adipogenesis, and the complex interactions between PPAR receptors and other adipogenic transcription factors such as CCAAT/enhancer-binding protein and PU.1 are explored. Because TZDs are clinically useful anti-diabetic insulin-sensitizing agents, it is clear that PPARγ is an important factor in the overall regulation of insulin action, and this area, including the tissue sites of action and the potential PPARγ target genes that mediate insulin sensitization, are reviewed. Although the effects of PPARγ ligands in causing insulin sensitization are the most well known, two other important areas of interest are reviewed, i.e. the roles of the PPARα receptor in atherosclerosis and oncogenesis. Evidence exists that PPARγ receptors can modulate the formation of foam cells in atherosclerotic plaques and that TZD treatment may be antiatherogenic. Furthermore, because this receptor promotes differentiation, it is proposed that it may inhibit oncogenic effects in various cell types. Consistent with this, mutations and translocations of the PPARγ receptor have been identified in human tumors, and this emerging area of PPARγ biology is examined and put into perspective in the review by Rosen and Spiegelman.

Cholesterol and sterol homeostasis is another important regulatory system closely controlled by nuclear receptor function, and in this series, Timothy L. Lu, Joyce J. Repa, and David J. Mangelesdorff provide a review on this subject entitled “Orphan Nuclear Receptors as eLiXIrS and FiXeRs of Sterol Metabolism” in which the two major nuclear receptors, LXR and FXR, involved in this regulatory system are reviewed. The role of the LXR nuclear receptor as a cholesterol sensor is discussed, including recent information covering target genes such as SREBP-I and the ATP binding cassette transporters, which facilitate efflux of cholesterol from cells. In the enterocyte, increased function of these ATP binding cassette transporters decreases cholesterol absorption from the gastrointestinal tract, and in macrophages, impaired function of these proteins may promote atherogenesis. The FXR bile acid sensor also plays a key role in overall sterol metabolism by regulating transcription of an array of genes involved in bile acid metabolism. The function of these two nuclear receptors is highly integrated, creating a complex but complementary physiologic network for controlling various facets of cholesterol and sterol metabolism across different tissues. Because of the importance of cholesterol metabolism in the etiology of atherosclerosis, this regulatory system offers a number of potential pharmaceutical targets for the development of new drugs to control hypercholesterolemia and favorably impact the process of atherosclerosis.

The final installment of this series covers another class of transcriptional regulators termed “orphan receptors” belonging to this large superfamily. The orphan nuclear receptors are proteins that share a great deal of structural similarity to NRs but do not have physiologic ligands that have been identified. At such time that a definitive ligand is identified, then that receptor would lose its orphan status. It is now known that several of these orphan receptors respond to xenobiotics in the environment that includes foreign chemicals such as environmental pollutants and prescription drugs. In response to xenobiotic compounds, these receptors mediate transcription of a variety of detoxifying enzymes that are members of the superfamly of cytochrome P450 (CYP) molecules. As Wen Xie and Ronald M. Evans point out in their review on this topic entitled “Orphan Nuclear Receptors: the Exotics of Xenobiotics,” this class of nuclear receptors represents the regulatory interface between the human genome and the external environment. This review discusses the major xenobiotic receptors, SXR, PXR, and CAR and points out that by inducing various CYP family members in response to specific xenobiotics, these receptors dictate our ability to metabolize different pharmaceutical compounds. An understanding of the function of these receptors should provide a mechanistic basis for drug interactions in which one drug alters the metabolism of another. Interestingly, the human SXR receptor and its rodent PXR orthologue display differential sensitivity to various xenobiotic agents, providing the basis for species specificity of xenobiotic responses. These workers go on to discuss a humanized mouse model expressing SXR, which should prove quite useful in preclinical studies of metabolism and toxicology for candidate pharmaceutical agents.

As is clear from the scope of these reviews, nuclear receptors participate in the regulation of almost all biologic processes. Thus, understanding the function of these receptors should be useful to a broad array of basic and clinical scientists. Because of their diverse biological effects, nuclear receptors have become major pharmaceutical targets in a host of disease states. Current pharmaceutical agents include natural hormonal ligands or their analogs such as glucocorticoids, thyroid hormone, and estrogens, as well as ligands for the PPARα and γ receptors. Undoubtedly, many more therapeutically useful pharmaceutical agents are on the horizon and will be entering the clinic in the near future.

REFERENCES

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