

Preface

It has been estimated that there are 48 nuclear receptor genes in the human genome. These code for a superfamily of proteins that can regulate gene transcription in response to a wide range of natural and synthetic ligands, including classical steroid hormones, vitamins, intermediate metabolites, xenobiotics and drugs. The first three-dimensional structures for isolated receptor domains appeared 25 years ago with the solution and crystal structures of the glucocorticoid and estrogen receptor DNA binding domains. The intervening years have seen an explosion in structures for the DNA and ligand binding domains of nearly all family members, culminating in the recent emergence of almost complete three-dimensional descriptions for nuclear receptor complexes bound to cognate response elements. These dramatic advances in structural analysis are paralleled by the growing evidence linking nuclear receptor function to normal physiological processes and disease. The insights gained from nuclear receptor structures have the potential to be translated into new drugs for major diseases, including cancer, metabolic syndrome and cardiovascular diseases.

In this book we have brought together a range of review articles to highlight current areas of nuclear receptor research, with the focus on structure and function and translational opportunities for drug discovery. In the first part, the attention is on receptor complexes (Chaps. 6 and 7), allosteric regulation and the role of the intrinsically disordered NTD (Chap. 5) and the role of DNA binding and response element architecture (Chap. 4).

This section also includes reviews on the corticosteroid receptors, glucocorticoid and mineralocorticoid (Chaps. 2 and 3) which are increasingly important clinically in disorders from hypertension and cardiovascular diseases to neurological disorders and cancers. In Part B the focus is on co-regulator protein structure and function. Nuclear receptors act primarily by promoting or disrupting the assembly of productive transcription complexes at target genes. Chapter 9 considers the role of intrinsically disordered structure again, in the assembly of co-repressor complexes by nuclear receptors. In Chap. 8, the attention is on a co-regulator of the androgen receptor that is restricted to primates. In the final section, the emphasis is on the

targeting of nuclear receptors with small molecules that could act in a tissue selective manner (Chap. 11) or target a novel pocket on the surface of the receptor (Chap. 10).

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