Preface

Nuclear Receptors: Past, Present, and Future

One of the major challenges in the postgenomic era is to understand the fundamental function and interplay of genes that build and maintain the organism. The availability of the complete human genome sequence, with the advent of bioinformatics tools and array technologies, has greatly accelerated this process. However, DNA sequence is inherently static and some have described the information as little more than a genomic "parts list." What is more relevant is knowing how groups or networks of genes are coordinately expressed to produce unique cell function and physiology. It is important to identify the functional interactions between genes, the connections within networks, and most importantly, the regulatory code, molecules, and mechanisms that direct this complex process.

Historically, the isolation and crystal structure of thyroid hormone by Kendall and Reichstein in 1914 and 1920, respectively, kicked off the first revolution in the field. This was soon followed by the isolation of vitamins A and D, bile acids, and the remaining steroid hormones between 1928 and 1952. However, how these bioactive lipids worked was clouded in mystery and the notion that they may all have a common mechanistic underpinning was never even suggested. Thus, the isolation of the glucocorticoid receptor cDNA in 1985 was critical, providing the first complete sequence of a nuclear receptor, a sequence that would prove to be a prototype of all subsequent family members.[5] This helped to trigger the next revolution in our understanding by providing a commonality of signaling by bioactive nuclear hormonal lipids.

We now know that nuclear hormone receptors (NRs) comprise a large family of ligand-modulated transcription factors (TFs) that mediate responses to a wide range of lipophilic signaling molecules including lipids, steroids, retinoids, hormones, and xenobiotics.[2,4,8] As sensors for these signals they provide an important link between transcriptional regulation and physiology. The NRs constitute one of the largest groups of TFs in animals (48 genes in humans, 49 in mice) and includes classic endocrine receptors that mediate the actions of the steroid hormones, thyroid hormones, and the fat-soluble vitamins A and D mentioned earlier, as well as a large number of so-called orphan

nuclear receptors, whose ligands, target genes, and physiological functions are still largely unknown. Thanks to recent intensive research, investigation of these orphans has revealed functions that are extremely interesting, particularly as it relates to normal physiology and pathologic states such as type 2 diabetes, heart disease, and cancer.

A series of key transformative advances were the isolation and characterization of the first nuclear receptor corepressors (SMRT and NCoR) and the coactivator (SRC-1),[3,7,9] respectively. This was quickly followed by the discovery that the histone acetyltransferase "CBP" was a nuclear receptor coactivator providing the first clear link between epigenetic modifications and hormone signaling.[1,6] These were the first critical steps in deconstructing the molecular logic as to how receptors interface with the chromatin template to regulate the transcriptional process itself. Eventually, more than 300 different NR-associated proteins have been isolated. About one third contains the prototypic "LXXLL" motif that suggests the potential for direct interaction with one or more NRs. Many of these proteins were identified as parts of cofactor complexes that often include between 8 and 20 proteins. If we add up the number of proteins involved in NR-directed activation, it would most likely fall between 50 and 100 although it could easily exceed these numbers in specialized situations. Furthermore, an equal number of proteins are most likely to be involved in target gene repression. In this odd way, while the hormone itself is a relatively simple structure, it becomes much easier to see how it achieves its regulatory complexity by employing standard association/dissociation kinetics to invoke dynamic allostery upon the cognate NR, resulting in the equally dynamic recruitment and dismissal of multiple coregulator complexes.

These key advances in turn lead us into our epigenomic future where receptor meets chromatin. The human and mouse genome projects opened up a great door but , as mentioned above, such projects provide a genetic parts list that is devoid of the instruction book. An understanding as to how the parts are called into action to create tissues, organs or complex physiology and disease is the next critical step in the field. The sequence helps to create a map of the chromosomes but receptors will provide a powerful tool to understand the process as to how the chromosomes are controlled. Why is this important? While there is only one genome in a person, there will be many "epigenomes" and this is where an understanding of complex physiologic processes will begin to emerge.

It is the goal of this book to highlight some of the newer breakthroughs, techniques, and challenges to position us for an exciting future.

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