Preface

While the effect of steroid hormones on various physiological processes has been recognized since the early twentieth century, it was only in the 1960s that the notion of specific hormone-binding proteins that transmit this signal in target tissues emerged. It is now over two decades since the first nuclear receptor—the glucocorticoid receptor—was cloned in the mid 1980s, which was quickly followed by the cloning of a number of additional receptors including those for thyroid hormone, estrogen, retinoids, and progesterone among others. The nuclear receptor superfamily now comprises a large family of ligand-activated transcription factors that include receptors for steroid and thyroid hormones, retinoids, vitamin D3, peroxisome proliferators, as well as "orphan" receptors that are essential for many physiological functions including cellular differentiation, growth, morphogenesis, apoptosis, and homeostasis. Nuclear receptors are modular proteins and share structural similarities in several regions. The most conserved domains include the DNA-binding domain (DBD) and the ligand-binding domain (LBD). Two separable transactivation domains have been identified: a ligand-dependent activation function (AF-2) located in the LBD, and a ligand-independent activation domain AF-1 located in the divergent A/B region.

Over the past two decades, the molecular mechanisms by which nuclear receptors are activated and initiate a transcriptional response have been defined. Steroid hormone receptors, which reside in the cytoplasm in complex with heat shock proteins, are transported to the nucleus on hormone binding, where they bind DNA as homodimers and transcriptionally regulate expression of target genes. Other receptors, such as retinoic acid receptors (RARs), thyroid hormone receptors (TRs), and peroxisome proliferator-activated receptor (PPAR), reside in the nucleus even in absence of ligand and bind DNA as heterodimers with their partner retinoid X receptor (RXR). In the absence of ligand, these receptors interact with corepressor molecules and actively repress transcription. Ligand binding results in a conformational change, which permits dissociation of corepressors and allows recruitment of coactivators that enhance the transcriptional activity of receptors. In addition to ligand-dependent transactivation, the transcriptional activity of nuclear receptors can be modulated by phosphorylation through cross talk with various signaling pathways. Nuclear receptors for which ligands have not been identified are classified as "orphan" receptors. This subfamily includes the chicken ovalbumin transcription factors (COUP-TFs), retinoid-related orphan receptors (RORs), and Ftz-F1 in *Drosophila*.

The advent of gene-disruption technologies have helped elucidate the functions of nuclear receptors *in vivo*. As our understanding of the biology

of nuclear receptors increases, so does our appreciation of the complexity of their actions. Since it is beyond the scope of any one book to cover all aspects of nuclear receptor biology, I have aimed to focus this book on the developmental roles of several nuclear receptors, as well as those of nuclear receptor coactivators and corepressors.

Thyroid hormone is critical for growth, development, and metabolism. Ng and Forrest provide a comprehensive review on the functions of TR with a specific focus on the developing auditory and visual systems. The chapter by Rotman et al. reviews the function of PPARα, PPARβ, and PPARγ in the formation of placenta, adipocytes, skin, and gut, and discusses potential roles in the nervous system.

Retinoic acid (RA), the active derivative of vitamin A, is critical for numerous aspects of development. Since both an excess and deficiency of RA can lead to severe developmental defects, embryonic RA levels are regulated by controlled synthesis and catabolism mediated by retinaldehyde dehydrogenases (RALDHs) and the cytochrome oxidase P450 subfamily 26 (CYP26) enzymes, respectively. The chapter by Pennimpede et al. covers our overall understanding of RA signaling and the functions of RARs and RXRs in embryonic development. In a related chapter, Niederreither and Dollé describe embryonic phenotypes related to loss of RALDH2, which is critical for RA synthesis *in vivo*.

Anterior–posterior (A–P) patterning of the hindbrain is dependent on retinoids. Hox genes, which are directly regulated by RA signaling, play a vital role in this process. The chapter by Glover et al. focuses on the role of endogenous retinoids and Hox genes in vertebrate hindbrain development. Similar to the hindbrain, RA and Hox genes are essential for vertebral A–P patterning. However, mesodermal Hox genes require an intermediary homeoprotein Cdx1, which is directly regulated by RA and Wnt signaling. Rhodes and Lohnes review the role of RA and Wnt signaling in regulation of Cdx1 and Hox genes in axial patterning.

The RA-responsive F9 embryonal carcinoma (EC) cell line has been used as a cell-autonomous model system to determine the role of RA signaling in endodermal differentiation. The chapter by Bour et al. covers our understanding of RAR function in primitive, parietal, and visceral endoderm formation, and how phosphorylation of specific residues in RARs is essential for the formation of these distinct cell types.

The chapter by Tang et al. discusses the functions of the orphan receptor COUP-TFI in the development of the nervous system. Jetten and Joo provide an extensive overview of RORα, RORβ, and RORγ in brain development, circadian rhythms, and development of secondary lymphoid tissues. They also discuss the role of DHR3, the ROR homologue in *Drosophila*, which regulates the nuclear receptor Ftz-F1. In a related chapter, Pick et al. review the role of Ftz-F1, an orthologue of the mammalian nuclear receptor SF-1, in metamorphosis and embryonic development. The protein partners

that interact with and modulate Ftz-F1 activity are discussed in relation to its function.

The last section of this book covers the role of nuclear receptor coregulators. Thompson and Beaudoin review the role of the corepressor Hairless, which interacts with TR, ROR, and vitamin D receptor (VDR) and is essential for skin function. Many coactivators including CBP/p300, the SRC-p160 family, the TRAP/DRIP/ARC complex, RIP140, and PGC-1 enhance the transcriptional activity of nuclear receptors. Reddy et al. provide a detailed review on the role of coactivators in modulating nuclear receptor function in differentiation and in metabolism.

This compilation of reviews represents a continuum of progress toward understanding the biological functions of the nuclear receptor superfamily. Recent developments include gene disruption studies of nuclear receptors and their cofactors, which has advanced our understanding of their roles in differentiation and development. In cases where embryonic or perinatal lethality has precluded full understanding of the biological functions, efforts are being directed to generate conditional mutants. Many additional issues are presently being addressed which include identification of molecular targets of nuclear receptors, defining the mechanisms by which cross talk with other signaling pathways modulates their function, and determining the role of various cofactors that positively or negatively regulate nuclear receptor activity in different cellular contexts. These ongoing studies will help define and understand the cellular and molecular basis of nuclear receptor function.

RESHMA TANEJA