

PREFACE

During the past five to ten years, a variety of tools has been developed in the disciplines of both gene engineering, and molecular and structural biology. Some of these advances have permitted scientists not only to identify and characterize genes, but also to target these genes by disruption, thus eliminating their function in living animals, and to determine the biological responses to altered gene products. This has particular significance in endocrine systems, in which feedback mechanisms between the hypothalamus, pituitary, and end organs are critical in normal physiology. Interpretation of the physiological significance, or the site of action of specific molecules in this context, has been difficult prior to transgenic technology. Major advances have occurred specifically in the areas of growth and development, and of reproduction.

Coupled with analysis of naturally occurring mutations in humans, the use of transgenic animals and in vitro systems has recently allowed endocrinologists to understand the importance of specific thyroid hormone receptor isoforms in vivo, the molecular basis for generalized resistance to thyroid hormones via mutations in the nuclear receptor, and mechanisms for suppressing gene transcription. Previously designated “orphan receptors,” such as steroidogenic factor-1, were demonstrated to have critical roles in development and reproduction. Other nuclear receptors—including those for thyroid hormone, estrogens, androgens, and progesterone—were shown to bind to coactivator and corepressor proteins that modified their transcriptional activity, and contributed to the cell-specific effects of the hormones. Previous dogma on the independence of steroid and peptide hormone mechanisms of action was shown to be simplistic. In fact, intracellular signaling pathways initiated by peptides modify steroid receptors directly and modulate their activity. These pathways also modify other transcription factors that, alone or in partnership with other proteins, regulate cell-specific patterns of gene expression. The application of transgenic and molecular techniques to the study of reproductive endocrinology illuminated the importance of estrogen in both males and females, the genetic basis for androgen insensitivity, gender-specific roles of the gonadotropins in normal reproduction, and the critical role played by activins, inhibins, and related growth factors.

In view of these tremendous advances, and the ability to draw clinical endocrine correlates from these findings, *Gene Engineering in Endocrinology* was assembled to include contributions from many leaders in these areas. The intent of our book is to place this new information in physiological perspective and to review the most recent work, as well as to indicate the areas of interest and questions that need still to be addressed in future research. The chapters describe studies performed with many types of molecular methods, and the use of animal and cellular model systems to explore the molecular basis of growth, development, and reproduction. Gene manipulation and disruption or “knock-out” results are discussed in the context of the impact of specific genes on these physiological systems, and the developmental or physiological time period at which the mutation becomes critical. The molecular studies are compared, when possible, with naturally occurring human and animal gene mutations, in order to compare complete elimination of gene function with an altered gene product.

Gene Engineering in Endocrinology is aimed at a broad spectrum of readers, including those who are currently interested and actively working in molecular endocrinology, and clinical endocrinologists interested in relating molecular mechanisms to clinical endocrinology.

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