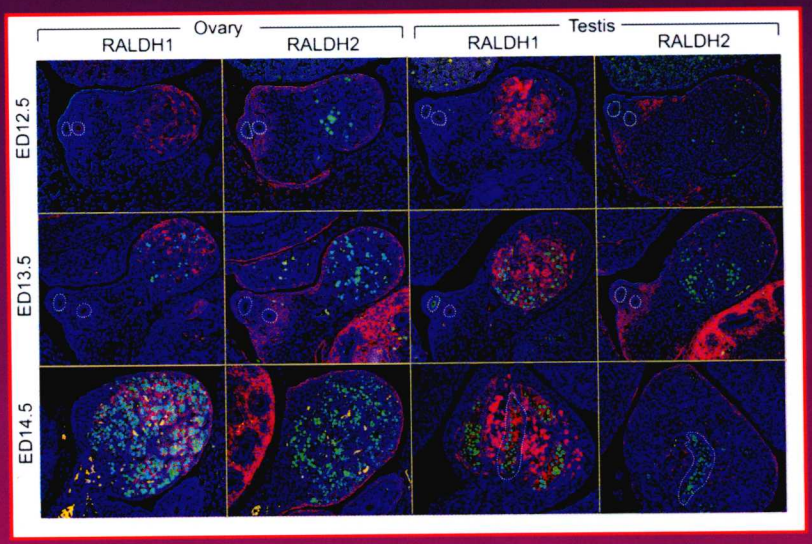
NUCLEAR RECEPTORS IN DEVELOPMENT AND DISEASE



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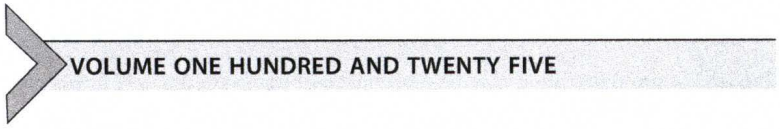

CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

Nuclear Receptors in Development and Disease

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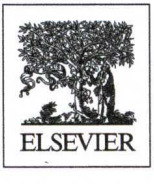

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"A meeting-ground for critical review and discussion of developmental processes"
A.A. Moscona and Alberto Monroy (Volume 1, 1966)

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PREFACE

Nuclear receptors form a large family of transcription factors whose functions and molecular mechanisms have been extensively studied over the past 30 years. A remarkable range of functions has been described for these receptors in many physiological systems, but somewhat less attention has focused on their roles in development. The articles in this volume attempt to cover various functions of nuclear receptors in development and their potential impact on diseases. The articles highlight not only differentiation and disease but also seek to give an evolutionary context for this superfamily of receptors. The article by Holzer, Markov, and Laudet presents an overview of the evolution of nuclear receptors and ligand signaling across animal species, whereas that by Jarvela and Pick discusses the function and evolution of nuclear receptors in insect species.

The next articles shift the focus onto mammalian systems and include the article by Zuo and Wan on the participation of a number of nuclear receptors in bone formation and remodeling. Several articles consider the roles of classical steroid hormone receptors and other receptors with defined ligands in the reproductive, nervous, endocrine, and other systems. Hamilton, Hewitt, Arao, and Korach discuss functions of the estrogen receptor, Busada and Cidlowski discuss the glucocorticoid receptor, and Wu and DeMayo discuss the progesterone receptor. Teletin, Vernet, Ghyselinck, and Mark describe the role of retinoic acid receptors in germ cell differentiation, whereas Flamant, Gauthier, and Richard focus on thyroid hormone receptors in brain development. The article by van Gucht, Moran, Meima, Visser, Chatterjee, Visser, and Peeters reviews recent findings on mutations in the *THRA* thyroid hormone receptor gene in human disease.

Several articles address the actions of orphan nuclear receptors and focus on differentiation in neuronal and other systems. Liu, Aramaki, Fu, and Forrest review the functions of the *RORB* retinoid-related orphan receptor gene in neuronal cell fate decisions and neurological disease, Sun, Cui, and Shi discuss the *TLX* orphan receptor in neurogenesis and neurodegeneration, and Yang, Feng, and Tang discuss *COUP-TF* genes in neurodevelopment and disease. The concluding articles discuss the roles of orphan receptors in other systems. Lin, Yang, Yang, Lin, Chang, Li, and Chang review the involvement of TR2/TR4 receptors in diverse tissues, and Xie, Wu, Tsai, and Tsai review the role of COUP-TF2 in muscle development.

We hope this volume will draw the attention of readers to the critical roles of nuclear receptors in development and will stimulate interest in the potential of these receptors as therapeutic targets for treatment of various diseases.

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CONTENTS

CHAPTER ONE

Evolution of Nuclear Receptors and Ligand Signaling: Toward a Soft Key–Lock Model?

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Contents

Abstract

Nuclear receptors (NRs) are a family of ligand-regulated transcription factors that modulate a wide variety of physiological functions in a ligand-dependent manner. The first NRs were discovered as receptors of well-known hormones such as 17β-estradiol, corticosteroids, or thyroid hormones. In these cases a direct activation of the receptor transcriptional activity by a very specific ligand, with nanomolar affinity, was demonstrated, providing a strong conceptual framework to understand the mechanism of action of these hormones. However, the discovery that some NRs are able to bind different ligands with micromolar affinity was a first sign that the univocal relationship between a specific receptor (e.g., TR) and a specific ligand (e.g., thyroid hormone) should not be generalized to the whole family. These discussions about the nature of NR ligands have been reinforced by the study of the hormone/receptor couple evolution. Indeed when the ligand is not a protein but a small molecule derived from a biochemical pathway, a simple coevolution mechanism between the ligand and the receptor cannot operate. We and others have recently shown that the ligands acting for a given NR early on during evolution were often different from the classical mammalian ligands. This suggests that the NR/ligand evolutionary relationship is more dynamic than anticipated and that the univocal relationship between a receptor and a specific molecule may be an

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