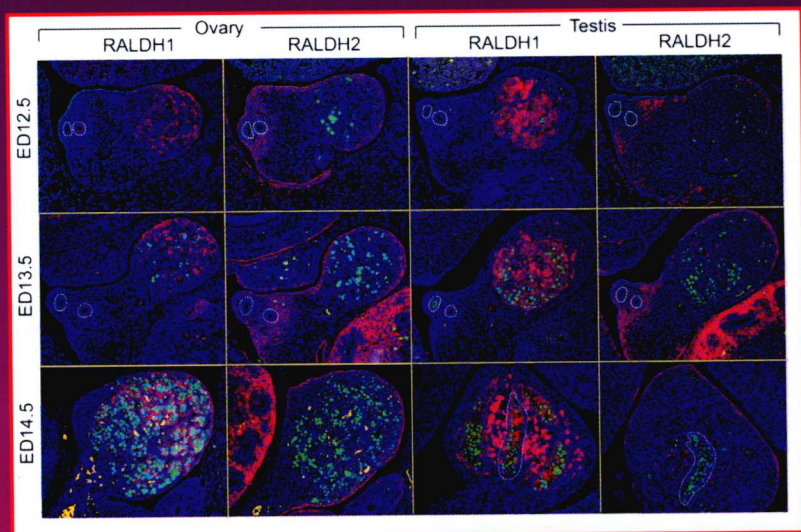


NUCLEAR RECEPTORS IN DEVELOPMENT AND DISEASE



Edited by

Douglas Forrest
Sophia Tsai



VOLUME ONE HUNDRED AND TWENTY FIVE

CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

Nuclear Receptors in Development and Disease

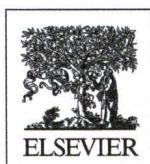
Edited by

DOUGLAS FORREST

*Laboratory of Endocrinology and Receptor Biology,
National Institute of Diabetes and Digestive and
Kidney Diseases (NIDDK),
National Institutes of Health (NIH), MD, United States*

SOPHIA TSAI

*Baylor College of Medicine,
Department of Molecular and Cellular Biology,
Program in Developmental Biology,
Houston, TX, United States*



ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
125 London Wall, London, EC2Y 5AS, United Kingdom

First edition 2017

Copyright © 2017 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-12-802172-9

ISSN: 0070-2153

For information on all Academic Press publications
visit our website at <https://www.elsevier.com/books-and-journals>



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

Publisher: Zoe Kruze

Acquisition Editor: Zoe Kruze

Editorial Project Manager: Shellie Bryant

Production Project Manager: Vignesh Tamil

Cover Designer: Greg Harris

Typeset by SPi Global, India



VOLUME ONE HUNDRED AND TWENTY FIVE

CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

Nuclear Receptors in Development
and Disease

CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

"A meeting-ground for critical review and discussion of developmental processes"

A.A. Moscona and Alberto Monroy (Volume 1, 1966)

SERIES EDITOR

Paul M. Wassarman

Department of Developmental and Regenerative Biology

Icahn School of Medicine at Mount Sinai

New York, NY, USA

CURRENT ADVISORY BOARD

Blanche Capel

Susan Mango

Wolfgang Driever

Philippe Soriano

Denis Duboule

Cliff Tabin

Anne Ephrussi

Magdalena Zernicka-Goetz

FOUNDING EDITORS

A.A. Moscona and Alberto Monroy

FOUNDING ADVISORY BOARD

Vincent G. Allfrey

Dame Honor B. Fell

Jean Brachet

John C. Kendrew

Seymour S. Cohen

S. Spiegelman

Bernard D. Davis

Hewson W. Swift

James D. Ebert

E.N. Willmer

Mac V. Edds, Jr.

Etienne Wolff

CONTRIBUTORS

Michihiko Aramaki

Laboratory of Endocrinology and Receptor Biology, NIDDK, National Institutes of Health, Bethesda, MD, United States

Yukitomo Arao

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences/NIH, Research Triangle Park, NC, United States

Jonathan T. Busada

Molecular Endocrinology Group, Signal Transduction Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, United States

Chawnshang Chang

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States; Sex Hormone Research Center, China Medical University/Hospital, Taichung, Taiwan

Hong-Chiang Chang

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States

Krishna Chatterjee

Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom

Alys M. Cheattle Jarvela

University of Maryland, College Park, MD, United States

John A. Cidlowski

Molecular Endocrinology Group, Signal Transduction Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, United States

Qi Cui

Beckman Research Institute of City of Hope; Irell & Manella Graduate School of Biological Sciences, Beckman Research Institute of City of Hope, Duarte, CA, United States

Francesco J. DeMayo

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC, United States

Su Feng

Institute of Life Science, Nanchang University, Nanchang, Jiangxi, China

Frédéric Flamant

Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS UMR 5242, INRA USC 1370, Ecole Normale Supérieure de Lyon, Lyon cedex, France

Douglas Forrest

Laboratory of Endocrinology and Receptor Biology, NIDDK, National Institutes of Health, Bethesda, MD, United States

Yulong Fu

Laboratory of Endocrinology and Receptor Biology, NIDDK, National Institutes of Health, Bethesda, MD, United States

Karine Gauthier

Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS UMR 5242, INRA USC 1370, Ecole Normale Supérieure de Lyon, Lyon cedex, France

Norbert B. Ghyselinck

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch; Centre National de la Recherche Scientifique (CNRS); Institut National de la Santé et de la Recherche Médicale (INSERM), Paris; Université de Strasbourg (UNISTRA), Strasbourg, France

Katherine J. Hamilton

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences/NIH, Research Triangle Park, NC, United States

Sylvia C. Hewitt

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences/NIH, Research Triangle Park, NC, United States

Guillaume Holzer

Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS, Ecole Normale Supérieure de Lyon, Lyon Cedex 07, France

Kenneth S. Korach

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences/NIH, Research Triangle Park, NC, United States

Vincent Laudet

Observatoire Océanologique de Banyuls-sur-Mer, UMR7232, Université Pierre et Marie Curie, Paris, Banyuls-sur-Mer, France

Gonghui Li

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States; Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China

Chang-Yi Lin

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States

Shin-Jen Lin

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States

Hong Liu

Laboratory of Endocrinology and Receptor Biology, NIDDK, National Institutes of Health, Bethesda, MD, United States

Manuel Mark

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch; Centre National de la Recherche Scientifique (CNRS); Institut National de la Santé et de la Recherche Médicale (INSERM), Paris; Université de Strasbourg (UNISTRA); Hôpitaux Universitaires de Strasbourg (HUS), Strasbourg, France

Gabriel V. Markov

Sorbonne Universités, UPMC Université Paris 06, CNRS, UMR 8227, Integrative Biology of Marine Models, Station Biologique de Roscoff, Place Georges Teissier, Roscoff Cedex, France

Marcel E. Meima

Erasmus University Medical Center, Rotterdam, The Netherlands

Carla Moran

Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom

Robin P. Peeters

Erasmus University Medical Center, Rotterdam, The Netherlands

Leslie Pick

University of Maryland, College Park, MD, United States

Sabine Richard

Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS UMR 5242, INRA USC 1370, Ecole Normale Supérieure de Lyon, Lyon cedex, France

Yanhong Shi

Beckman Research Institute of City of Hope; Irell & Manella Graduate School of Biological Sciences, Beckman Research Institute of City of Hope, Duarte, CA, United States

Guoqiang Sun

Beckman Research Institute of City of Hope, Duarte, CA, United States

Ke Tang

Institute of Life Science, Nanchang University, Nanchang, Jiangxi, China

Marius Teletin

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch; Centre National de la Recherche Scientifique (CNRS); Institut National de la Santé et de la Recherche Médicale (INSERM), Paris; Université de Strasbourg (UNISTRA); Hôpitaux Universitaires de Strasbourg (HUS), Strasbourg, France

Ming-Jer Tsai

Baylor College of Medicine; Program in Developmental Biology, Baylor College of Medicine, Houston, TX, United States

Sophia Tsai

Baylor College of Medicine; Department of Molecular and Cellular Biology, Program in Developmental Biology, Baylor College of Medicine, Houston, TX, United States

Anja L.M. van Gucht

Erasmus University Medical Center, Rotterdam, The Netherlands

Nadège Vernet

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch; Centre National de la Recherche Scientifique (CNRS); Institut National de la Santé et de la Recherche Médicale (INSERM), Paris; Université de Strasbourg (UNISTRA), Strasbourg, France

Theo J. Visser

Erasmus University Medical Center, Rotterdam, The Netherlands

W. Edward Visser

Erasmus University Medical Center, Rotterdam, The Netherlands

Yihong Wan

The University of Texas Southwestern Medical Center, Dallas, TX, United States

San-Pin Wu

Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC, United States

Xin Xie

Baylor College of Medicine, Houston, TX, United States

Dong-Rong Yang

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States; The Second Affiliated Hospital of Suzhou University, Suzhou, China

Guosheng Yang

George Whipple Lab for Cancer Research, The Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States; Guangdong 2nd Provincial People's Hospital, Guangzhou, China

Xiong Yang

Institute of Life Science, Nanchang University, Nanchang, Jiangxi, China

Hao Zuo

The University of Texas Southwestern Medical Center, Dallas, TX, United States

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.

DOUGLAS FORREST

Laboratory of Endocrinology and Receptor Biology,
National Institute of Diabetes and Digestive
and Kidney Diseases (NIDDK),
National Institutes of Health (NIH), MD, United States

SOPHIA TSAI

Baylor College of Medicine,
Department of Molecular and Cellular Biology,
Program in Developmental Biology,
Houston, TX, United States

CONTENTS

<i>Contributors</i>	<i>xi</i>
<i>Preface</i>	<i>xv</i>
1. Evolution of Nuclear Receptors and Ligand Signaling: Toward a Soft Key–Lock Model?	1
Guillaume Holzer, Gabriel V. Markov, and Vincent Laudet	
1. Introduction	2
2. The Ligand–Receptor Couple for NRs	11
3. NR Diversification During Animal Evolution	18
4. Evolution of Ligand Binding	20
5. Alternative Ligands	25
6. Generalization	28
References	30
2. The Function and Evolution of Nuclear Receptors in Insect Embryonic Development	39
Alys M. Cheadle Jarvela and Leslie Pick	
1. Introduction: Nuclear Receptor Structure and Function	40
2. Roles of NRs in <i>Drosophila</i> Embryonic Development	42
3. Functional Analysis of NRs in Nonmodel Insects	55
Acknowledgments	61
References	61
3. Nuclear Receptors in Skeletal Homeostasis	71
Hao Zuo and Yihong Wan	
1. Introduction	72
2. NRs and Bone Homeostasis	74
3. Conclusions	91
Acknowledgments	94
References	94
4. Estrogen Hormone Biology	109
Katherine J. Hamilton, Sylvia C. Hewitt, Yukitomo Arao, and Kenneth S. Korach	
1. Introduction	110
2. Cell Mechanisms	110

3. Uterine Estrogen Response	114
4. ER in the Ovary	126
5. ER in Metabolism	137
References	140
5. Mechanisms of Glucocorticoid Action During Development	147
Jonathan T. Busada and John A. Cidlowski	
1. Introduction	147
2. Adrenal Gland Morphology and Embryology	148
3. Production and Metabolism of Glucocorticoids in the Adult and the Fetus	151
4. Signaling and Function of the Glucocorticoid Receptor	155
5. The Impact of Glucocorticoid Signaling on Fetal Development	159
6. Concluding Remarks	163
Acknowledgment	163
References	163
6. Progesterone Receptor Signaling in Uterine Myometrial Physiology and Preterm Birth	171
San-Pin Wu and Francesco J. DeMayo	
1. Introduction	171
2. Ligand Availability	173
3. Composition of PGR Isoforms	175
4. The PGR–NF- κ B Axis	178
5. The PGR-ZEB-MicroRNA Regulatory Circuit	179
6. Endoplasmic Reticulum Stress and Unfolded Protein Response	182
7. Concluding Remarks and Future Perspectives	183
Acknowledgment	185
References	185
7. Roles of Retinoic Acid in Germ Cell Differentiation	191
Marius Teletin, Nadège Vernet, Norbert B. Ghyselinck, and Manuel Mark	
1. Introduction	193
2. ATRA Signaling in the Fetal Gonads	196
3. ATRA Signaling Is Instrumental to Spermatogonia Differentiation in the Prepubertal and Adult Testis	204
4. ATRA Signaling Is Instrumental to Meiosis in Spermatocytes	209
5. ATRA Metabolism Within the SE Controls the Timing and Spatial Patterning of Spermatogonia Differentiation	210

6. Male GC Are Both Direct and Remote Targets of ATRA Action: Lessons From Mouse Mutants Lacking Retinoid Receptors	214
7. Concluding Remarks	219
Acknowledgments	220
References	220
8. Retinoid-Related Orphan Receptor β and Transcriptional Control of Neuronal Differentiation	227
Hong Liu, Michihiko Aramaki, Yulong Fu, and Douglas Forrest	
1. Introduction	228
2. The <i>Rorb</i> Gene and ROR β Protein Isoforms	229
3. Response Elements for ROR β Proteins	232
4. Mouse Strains With <i>Rorb</i> Mutations	233
5. Expression Patterns of the <i>Rorb</i> Gene in the Nervous System	233
6. The <i>Rorb</i> Gene and Neuronal Differentiation	237
7. <i>Rorb</i> and Differentiation in the Cerebral Cortex	237
8. <i>Rorb</i> and Differentiation in the Retina	239
9. Partners in Plasticity: A Combinatorial Model for Differentiation	243
10. The <i>RORB</i> Gene and Human Disease	245
11. Circadian Rhythms, Locomotion, and Other Functions	246
12. Potential Ligands for ROR β Proteins	248
13. Concluding Remarks	249
Acknowledgment	250
References	250
9. Nuclear Receptor TLX in Development and Diseases	257
Guoqiang Sun, Qi Cui, and Yanhong Shi	
1. Introduction	257
2. TLX in Development and Diseases	259
3. Perspectives	267
Acknowledgments	268
References	268
10. <i>COUP-TF</i> Genes, Human Diseases, and the Development of the Central Nervous System in Murine Models	275
Xiong Yang, Su Feng, and Ke Tang	
1. Introduction	277
2. <i>COUP-TF</i> Genes and Human Diseases	277
3. Brief Overview of the Early CNS Development	279

4. <i>COUP-TF</i> Genes and the Development of Dorsal Forebrain	280
5. <i>COUP-TF</i> Genes and the Development of Ventral Forebrain	284
6. <i>COUP-TFII</i> Gene and the Development of Cerebellum	288
7. <i>COUP-TF</i> Genes and Gliogenesis	288
8. <i>COUP-TF</i> Genes and Neural Crest Cells	290
9. <i>COUP-TF</i> Genes and Adult Neuronal Stem Cells	291
10. Conclusion and Perspectives	291
Acknowledgments	293
References	293

11. Genetic Investigation of Thyroid Hormone Receptor Function in the Developing and Adult Brain **303**

Frédéric Flamant, Karine Gauthier, and Sabine Richard

1. Introduction	303
2. TRs in the Brain	305
3. Animal Models With TR Mutations	307
4. Interpretation of Phenotypes Resulting From Knock-In and Knock-Out Mutations	310
5. Respective Functions of TRs in Neural Cell Differentiation	314
6. Nongenomic Signaling in the Brain	318
7. The Origin of Phenotype Variability	320
8. Distinction Between Developmental and Adult Functions of TRs in the Brain	322
9. TR Target Genes Definition	323
10. T3 Target Gene Functions	325
Acknowledgment	327
References	327

12. Resistance to Thyroid Hormone due to Heterozygous Mutations in Thyroid Hormone Receptor Alpha **337**

Anja L.M. van Gucht, Carla Moran, Marcel E. Meima, W. Edward Visser, Krishna Chatterjee, Theo J. Visser, and Robin P. Peeters

1. Introduction	338
2. Molecular Mechanisms Underlying RTH α	340
3. Clinical Phenotype	343
4. Pathogenesis	346
5. Treatment	348
6. Conclusions	351
Acknowledgments	351
References	351

13. TR2 and TR4 Orphan Nuclear Receptors: An Overview	357
Shin-Jen Lin, Dong-Rong Yang, Guosheng Yang, Chang-Yi Lin, Hong-Chiang Chang, Gonghui Li, and Chawnshang Chang	
1. Introduction	359
2. Ligands/Activators That Transactivate TR4	360
3. TR4 Downstream Target Genes	363
4. TR4 Roles in PPAR γ -Related Diseases and Their Impacts on Drug Development	365
5. Summary and Future Perspectives	368
Acknowledgment	369
References	369
14. The Role of COUP-TFII in Striated Muscle Development and Disease	375
Xin Xie, San-Pin Wu, Ming-Jer Tsai, and Sophia Tsai	
1. Introduction	376
2. COUP-TFII Functions in Skeletal Muscle Development	377
3. COUP-TFII Functions in Skeletal Muscle Regeneration	380
4. COUP-TFII Hyperactivity, SC Dysfunction, and Muscular Dystrophy	386
5. COUP-TFII Functions in Cardiac Muscle Development	387
6. COUP-TFII Overexpression, Mitochondria Dysfunction, and Heart Failure	392
7. Concluding Remarks and Future Perspectives	393
Acknowledgments	395
References	395



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

Guillaume Holzer*, Gabriel V. Markov[†], Vincent Laudet^{*,1}

*Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS, Ecole Normale Supérieure de Lyon, Lyon Cedex 07, France

[†]Sorbonne Universités, UPMC Université Paris 06, CNRS, UMR 8227, Integrative Biology of Marine Models, Station Biologique de Roscoff, Place Georges Teissier, Roscoff Cedex, France

^{*}Observatoire Océanologique de Banyuls-sur-Mer, UMR7232, Université Pierre et Marie Curie, Paris, Banyuls-sur-Mer, France

¹Corresponding author: e-mail address: vincent.laudet@obs-banyuls.fr

Contents

1. Introduction	2
2. The Ligand–Receptor Couple for NRs	11
3. NR Diversification During Animal Evolution	18
4. Evolution of Ligand Binding	20
5. Alternative Ligands	25
6. Generalization	28
References	30

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