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Essays in Biochemistry

The Nuclear Receptor Superfamily

Edited by I.J. McEwan

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Contents

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Preface.....

Authors.....

Abbreviations.....

1 Sex, drugs and gene expression: signalling by members of the nuclear receptor superfamily

Iain J. McEwan

Abstract	1
Introduction	1
“Evolution... is a change from an indefinite, incoherent homogeneity, to a defined coherent heterogeneity” Herbert Spenser (<i>First Principles</i>).....	2
“What is the character of a family to a hypothesis?” Laurence Sterne (<i>Tristram Shandy</i>).....	2
“Action is transitory, — a step, a blow...” William Wordsworth (<i>The Borders</i>)	6
“Accidents will occur in the best-regulated families” Charles Dickens (<i>David Copperfield</i>)	7
Conclusions and future perspectives	8
Summary	9
References.....	9

2 The evolution of the nuclear receptor superfamily

Héctor Escriva, Stéphanie Bertrand and Vincent Laudet

Abstract	11
Introduction.....	11
Appearance and diversification of the NR superfamily	13
Evolution of the NRs functional characteristics.....	17
Comparative genomics of NRs	20
Conclusions and perspectives	22
Summary.....	23
References.....	24

3	Overview of the structural basis for transcription regulation by nuclear hormone receptors	
	<i>Raj Kumar, Betty H. Johnson, and E. Brad Thompson</i>	
	Abstract.....	27
	Introduction.....	28
	NTD.....	30
	DBD.....	33
	LBD.....	34
	NHRs and co-regulatory proteins.....	36
	Conclusions.....	37
	Summary.....	37
	References.....	38
4	Role of molecular chaperones in steroid receptor action	
	<i>William B. Pratt, Mario D. Galigniana, Yoshihiro Morishima and Patrick J. M. Murphy</i>	
	Abstract.....	41
	Introduction.....	41
	Hsp90 acts on the ligand-binding domain (LBD) of steroid receptors....	42
	Assembly of receptor–hsp90 heterocomplexes.....	44
	Mechanism of cleft opening.....	47
	Hsp90 and GR function <i>in vivo</i>	50
	Conclusion.....	56
	Summary.....	56
	References.....	57
5	DNA recognition by nuclear receptors	
	<i>Frank Claessens and Daniel T. Gewirth</i>	
	Abstract.....	59
	Introduction.....	60
	The HREs.....	61
	The DBDs.....	63
	Discrimination of the core hexamers.....	63
	Dimerization controls specificity.....	66
	Exceptions to the rules.....	67
	Allosteric effects of HREs.....	68
	Other functions of the DBD.....	69
	General conclusions.....	69
	Summary.....	70
	References.....	70

6 Transcriptional activation by nuclear receptors

Mari Luz Acevedo and W. Lee Kraus

Abstract	73
Introduction.....	73
Chromatin: the physiological template for NR-dependent transcription	74
The RNA pol II transcriptional machinery	74
NR co-activators: distinct classes with multiple activities	76
Histone modifications and the histone code	80
Cofactor recruitment and activity at NR-regulated promoters.....	81
Shutting off NR-dependent transcription: factor modification, recycling, redistribution and turnover	84
Cell-type-specificity and co-integration of multiple signalling pathways..	85
Conclusion	86
Summary.....	86
References.....	87

7 Gene repression by nuclear hormone receptors

Udo Moebren, Maren Eckey and Aria Baniabmad

Abstract	89
Introduction.....	90
Gene-silencing by co-repressors	90
NHR action on chromatin.....	94
Gene silencing by NHRs through interference with the basal transcription machinery.....	96
Hormone receptor inactivation by anti-hormones	96
Negative response elements.....	97
Transcriptional repression by NHR through inhibition of signalling pathways via crosstalk.....	98
Impact of gene repression by NHRs on development and disease.....	100
Conclusions	101
Summary.....	101
References	101

8 Receptor mechanisms of rapid extranuclear signalling initiated by steroid hormones

Viroj Boonyaratanakornkit and Dean P. Edwards

Abstract.....	105
Introduction.....	106
Extranuclear signalling actions of progesterone: classical intracellular progesterone receptor (PR).....	107

Extranuclear progesterone signalling: role of a novel mPR.....	110
Extranuclear signalling of oestrogen: role of the classical ER.....	112
Extranuclear signalling actions of oestrogen: role of novel membrane receptors?.....	113
Cell-membrane localization of a subpopulation of classical ERs.....	114
The role of extranuclear ER signalling <i>in vivo</i>	115
Conclusions.....	116
Summary.....	117
References.....	118

9 Nuclear receptors and disease: androgen receptor

*Bruce Gottlieb, Lenore K. Beitel, Jianhui Wu, Youssef A. Elhaji
and Mark Trifiro*

Abstract.....	121
Introduction.....	122
Structure–function relationships of the AR protein and gene.....	122
Diseases as a result of mutations in the AR gene.....	125
Diseases directly associated with AR CAG repeat-length variation: spinothalamic muscular atrophy (SBMA; Kennedy disease).....	130
AR CAG tract-length variation as a risk factor for disease.....	131
Conclusions.....	134
Summary.....	134
References.....	135

10 Glucocorticoid and mineralocorticoid receptors and associated diseases

Tomoshige Kino and George P. Chrousos

Abstract.....	137
Introduction.....	138
Structure and actions of GRs and MRs.....	139
Natural physiological steroid hormone ‘resistance’ in animals.....	143
Pathological changes of GR and MR activities in humans.....	144
Conclusions.....	152
Summary.....	153
References.....	153

11 Nuclear receptors in disease: the oestrogen receptors

Maria Nilsson, Karin Dahlman-Wright and Jan-Åke Gustafsson

Abstract.....	157
The oestrogen receptors (ERs).....	158
ER modulators in physiology and disease.....	159
ERs and breast cancer.....	159
ERs and prostate cancer.....	160
ERs and cardiovascular disease.....	161
ERs and osteoporosis.....	161
ERs and diseases of the central nervous system (CNS).....	162
ERs and diseases of the immune system.....	162
ER polymorphisms and mutations in relation to disease.....	162
Conclusion.....	164
Summary.....	165
References.....	165

12 Nuclear receptors and human disease: thyroid receptor β , peroxisome-proliferator-activated receptor γ and orphan receptors

Mark Gurnell and V. Krishna K. Chatterjee

Abstract.....	169
Introduction.....	170
TR β and the syndrome of resistance to thyroid hormone (RTH).....	173
PPAR γ and the syndrome of PPAR γ ligand resistance (PLR).....	177
HNF4 α and MODY1.....	181
SHP and obesity.....	182
SFI and DAX1 in disorders of gonadal and adrenal development.....	183
PNR and enhanced S-cone syndrome (ESCS).....	184
NURR1 and abnormalities of dopaminergic neurotransmission: familial Parkinson's disease and schizophrenia/manic-depressive disorder.....	185
Conclusions.....	186
Summary.....	186
References.....	187

Subject index.....	191
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Communication between cells is of central importance in multicellular organisms. Indeed, it could be argued that it is one of the defining features of multicellularity, as it allows for cell specialization and cell organization into tissues in a controlled and regulated manner. Nuclear receptors are a large family of signalling proteins that play crucial roles during embryonic development and in the regulation of reproductive and metabolic functions in the adult.

Nuclear receptors share a common architecture at the protein level, but a remarkable diversity is observed in terms of natural ligands and xenobiotics that bind to and regulate receptor function. The defining feature of the ligands is that they are small, lipophilic molecules that are thought to diffuse across the plasma membrane. Nuclear receptors act by regulating the patterns of gene expression in target cells and can be thought of as 'ligand-activated' transcription factors. However, a significant proportion of family members have been described as 'orphans' as the natural ligand, if it exists, remains to be identified. This volume of *Essays in Biochemistry* focuses on recent exciting developments in nuclear receptor action, as well as highlighting future research goals. It is timely, as it is almost 20 years since the first steroid receptor cDNAs were cloned, and over 45 years since the first clues were uncovered as to the molecular actions of what turned out to be a large family of diverse signalling proteins.

After a brief overview of the area, the volume starts with a discussion on the evolution of the functional diversity that is found within the nuclear receptor superfamily by Laudet and colleagues. These authors also consider what information can be gained from comparative genome-wide analysis. There then follows two essays that examine the structure–function relationships, by Thompson and colleagues, and by Claessens and Gewirth. The latter authors focus on the DNA-binding properties of family members. The distinct roles that protein–protein interactions play in nuclear receptor action are considered by essays on molecular chaperone complexes (Pratt and colleagues), co-activator complexes (Acevedo and Kraus), co-repressor complexes (Banahmad and colleagues) and the extranuclear actions of progesterone and oestradiol receptors (Boonyaratanakornkit and Edwards). The preceding discussions on the structure and biochemical properties of nuclear receptors lead into the final four essays on the androgen receptor (Trifiro and colleagues), glucocorticoid and mineralocorticoid receptors (Kino and Chrousos), oestrogen receptors (Gustafsson and colleagues), and thyroid hormone receptors, peroxisome-proliferator-activated receptors and orphan receptors (Gurnell and Chatterjee). These essays address the question of the physiological roles of different

nuclear receptors and how genetic alterations in receptor proteins disrupts signalling and underpins a diverse range of pathological conditions, including cancers, reproductive and developmental defects, and metabolic disorders, such as diabetes and obesity.

I would like to express my sincere thanks to the authors for their excellent contributions and discussing their individual areas of expertise in a clear and erudite manner. I am also grateful to the many reviewers for their constructive comments and suggestions on the submitted manuscripts. It was my aim at the beginning of this enterprise that this volume would be accessible and of benefit to both undergraduate and postgraduate students, as well as their teachers, in the biological and medical science disciplines, who wish to learn about nuclear receptors. Now that it is complete, I hope those already working in nuclear receptor research will also find the topics covered of interest and stimulating. My thanks also go to Mike Cunningham and Portland Press Ltd for their hard work and diligence in ensuring the high quality of this book.

Iain J. McEwan
Aberdeen, UK
April 2004

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Iain McEwan's scientific career began in Glasgow as an undergraduate student at the University of Strathclyde, graduating in 1983 with a first in Biochemistry (B.Sc.), before obtaining a Ph.D. degree from the University of Glasgow in 1997. He has worked as a research fellow at the Friedrich Miescher Institute in Basel, Switzerland, and the Karolinska Institute in Stockholm, Sweden. He was appointed to a lectureship at the University of Aberdeen in 1997, where he is currently a Senior Lecturer in the School of Medical Sciences. His research focuses on the molecular mechanisms of action of the androgen receptor in health and disease, and his group is particularly interested in understanding the dynamic relationships between receptor conformation and interactions with protein-binding partners and DNA-response elements.

Hector Escriva studied biology at the Universitat de Valencia, Spain, and then moved to the Institut Pasteur de Lille, France, where he undertook a Ph.D. in molecular parasitology, entitled 'Nuclear receptors in *Schistosoma mansoni*: molecular cloning and characterization of an RXR homolog. Molecular phylogeny of the nuclear receptor superfamily'. At present he is working on the evolution of the nuclear receptor superfamily as a CNRS Research Scientist at the Ecole Normale Supérieure de Lyon, France. **Stéphanie Bertrand** studied biology at the Université de Lyon, France. She worked towards a Masters thesis on amphibian metamorphosis and she is now working on her Ph.D. at the Ecole Normale Supérieure de Lyon, on the comparative genomics of the nuclear hormone receptor superfamily. **Vincent Laudet** studied biochemistry at the Université Louis Pasteur de Strasbourg, France. He did a Ph.D. in the Laboratoire d'Oncologie Moléculaire at the Institut Pasteur de Lille, France, on the structure and evolution of the nuclear hormone receptors. After his Ph.D., he worked for several years as a CNRS Research Scientist at the Institut Pasteur de Lille, and then he moved to the Ecole Normale Supérieure de Lyon as a Professor and where he is now the group leader of the Structure and Evolution of the Nuclear Hormone Receptors Group.

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William Pratt, M.D., is Professor of Pharmacology at the University of Michigan, Ann Arbor, MI. He has worked in the field of steroid-hormone action for 40 years, and together with Etienne Baulieu and David Toft, he discovered the interaction of hsp90 with steroid receptors. **Mario Galigniana**, Ph.D., is an Assistant Research Scientist at the University of Michigan. He has worked on mineralocorticoid and glucocorticoid receptors for 15 years, and over the past 9 years, he has determined roles for hsp90 and hsp90-bound immunophilins in glucocorticoid receptor translocations from the cytoplasm to the nucleus. **Yoshihiro Morishima**, M.D., Ph.D., is a Postdoctoral Researcher at the University of Michigan. He has spent the last 6 years working on the mechanism of assembly of glucocorticoid receptor-hsp90 hetero-complexes. **Patrick Murphy**, Ph.D., is a Postdoctoral Researcher at the University of Michigan. For the past 5 years, he has worked on the stoichiometry and structure of the hsp90/hsp70-based chaperone machinery.

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Mari Luz Acevedo graduated from the University of Puerto Rico, Rio Piedras, with a B.S. She is a senior doctoral candidate in the Graduate Field of Biochemistry, Molecular and Cell Biology at Cornell University, Ithaca, NY, and is minoring in pharmacology. Her thesis project is an investigation of the role of co-activators in transcriptional regulation by the oestrogen receptor. Her graduate studies are funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a part of the National Institutes of Health. **W. Lee Kraus** obtained an M.S. and a Ph.D. from the University of Illinois, Champaign-Urbana, IL. He has been an Assistant Professor in the

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Udo Moehren obtained his Master of Science degree in biology at the Justus-Liebig University, Giessen, Germany, where he is currently working as a postgraduate student in Aria Baniahmad's group. His research interests are the molecular mechanisms of anti-hormone action on the androgen receptor and the involvement of co-repressors. **Maren Eckey** studied biology at the Justus-Liebig University, and completed her degree with a laboratory diploma thesis (Masters of Sciences) based on the analysis of gene silencing by thyroid hormone receptors and the co-repressor Alien. As a graduate student, she continued to work in this field with Aria Baniahmad, analysing novel repression mechanisms mediated by the co-repressor Alien on the chromatin level. **Aria Baniahmad** studied biology at the University of Würzburg and the University of Hohenheim, Germany. He was awarded a Ph.D. at the Max-Planck-Institute for Biochemistry in Munich, Germany, for identifying the repressive regulation by thyroid hormone and retinoic acid receptors. He then joined Bert O'Malley's lab at Baylor College of Medicine, Houston, TX, U.S.A. After moving back to Germany, he became independent group leader and principal investigator at the Justus-Liebig University, whose work analyses gene-silencing mechanisms by nuclear hormone receptors.

Viroj Boonyaratanakornkit received a degree in Medical Technology from Chulalongkorn University, Bangkok, Thailand, in 1988 and a Ph.D. from Loma Linda University, CA, U.S.A., in 1996. He then moved to the University of Colorado Health Sciences Center, Denver, CO, as a post-doctoral fellow and is currently an Instructor in the Department of Pathology. **Dean P. Edwards** is graduated with a B.S. in zoology from Ohio University, Athens, OH, in 1969. He received a Ph.D. from the Medical College of Georgia, Augusta, GA, in 1976 and followed this as a research fellow at the University of Texas, San Antonio, TX, working on steroid receptors and breast cancer. He is currently a Professor at the Department of Pathology, in the School of Medicine at the University of Colorado Health Sciences Center, Denver, CO, where his research continues to focus on steroid receptors and hormone action in breast cancer.

Bruce Gottlieb, Ph.D., is a geneticist/molecular biologist who is the curator of the Androgen Receptor Gene Mutations Database and is particularly interested in the development of gene-mutation databases and the utilization

of computer modelling to relate protein structure to function. He is a project director at the Lady Davis Institute for Medical Research, Montréal, Canada, an Adjunct Professor in the Faculty of Medicine at McGill University, Montréal, Canada, and a Professor of Biology at John Abbott College, Ste. Anne de Bellevue, Canada. **Lenore K. Beitel**, Ph.D., is a biochemist/molecular biologist who is interested in many aspects of the structure–function relationship of the androgen receptor and, in particular, with androgen-receptor-interacting proteins, and spinobulbar muscular atrophy. She is a research scientist at the Lady Davis Institute for Medical Research and an Assistant Professor in the Faculty of Medicine at McGill University. **Janbui Wu**, Ph.D., is a chemist that is interested in using computer-generated molecular dynamic modelling to predict the effect of mutations on protein structure and function. He is a project director at the Lady Davis Institute for Medical Research and an Assistant Professor in the Department of Oncology at McGill University. **Yossef Elhaji**, M.Sc., is a Ph.D. candidate in the Department of Human Genetics at McGill University. **Mark Trifiro**, M.D., is a clinical and research molecular endocrinologist, and heads the Molecular Endocrinology Laboratory at the Lady Davis Institute for Medical Research. He is an Associate Professor of Medicine at McGill University.

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Mark Gurnell trained as an undergraduate at St Bartholomew's Hospital, London, and it was there that he first developed his interest in endocrinology

under the combined tutorships of Professors G.M. Besser, J.A.H. Wass and A.B. Grossman. His interest in the molecular basis of endocrine disorders subsequently took him to St John's College, Cambridge as a Wellcome Training Fellow under the supervision of Professor V.K.K. Chatterjee, where he completed his Ph.D. entitled 'The roles of the human thyroid hormone β receptor and the peroxisome-proliferator-activated receptor γ (PPAR γ) in human disease'. Having completed his clinical training in Cambridge, he has continued to work in close collaboration with Professor Chatterjee, exploring the roles of orphan nuclear receptors in human metabolism. **V. Krishna K. Chatterjee** was an undergraduate at Cambridge and completed his clinical training in Oxford. He trained as an endocrinologist at the Hammersmith Hospital, London and subsequently undertook research in the Thyroid Unit at Massachusetts General Hospital, Boston, MA, with Professor Larry Jameson. In 1990, he returned to the Department of Medicine at Cambridge as a Wellcome Senior Clinical Research Fellow and was appointed Professor of Endocrinology there in 1998. His research interests include the syndrome of resistance to thyroid hormone and defects in nuclear hormone receptors (including PPAR γ) in human disorders. He is also evaluating the role of DHEA (dehydroepiandrosterone) hormone replacement in adrenal insufficiency.

Abbreviations

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AD	activation domain
AF	activation function
Aha	activator of heat-shock protein 90 ATPase
AHC	adrenal hypoplasia congenita
AIS	androgen-insensitivity syndrome
AP-1	activator protein 1
APML	acute promyelocytic leukaemia
AR	androgen receptor
ARKO	aromatase-knockout
ASSC	amiloride-sensitive sodium channel
AVP	arginine vasopressin
BAG-1	Bcl-2-associated gene product-1
BMD	bone mineral density
Brg1	brahma-related gene-1
CAIS	complete androgen-insensitivity syndrome
CaP	prostate cancer
CAR	constitutive androstane receptor
CARM	co-activator-associated arginine methyltransferase
CBP	cAMP-response-element-binding protein-binding protein
CHIP	C-terminus of heat-shock-protein-70-interacting protein
ChIP	chromatin immunoprecipitation
CHO	Chinese-hamster ovary cells
CNS	central nervous system
COUP-TF	chicken ovalbumin upstream promoter-transcription factor 1
CRC	chromatin-remodelling complex
CREB	cAMP-response-element-binding protein
CRH	corticotropin-releasing hormone
CTE	C-terminal extension
CVD	cardiovascular disease
CyP	cyclophilin
DAX1	dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region on the X chromosome gene 1
DBD	DNA-binding domain

D-box	distal box
DR	direct repeat
EcR	ecdysone receptor
EGF	epidermal growth factor
eNOS	endothelial nitric oxide synthase
ER	oestrogen receptor
ERK	extracellular-signal-regulated kinase
ERKO	oestrogen-receptor-knockout
ERR	oestrogen-related receptor
ESCS	enhanced S-cone syndrome
FKBP	FK506-binding protein
FTZ-F1	fushi tarazu factor 1
FXR	farnesoid X receptor
GCNF	germ cell nuclear factor
GPCR	G-protein-coupled receptor
GR	glucocorticoid receptor
GRE	glucocorticoid-response element
GRTH	generalized resistance to thyroid hormone
HAT	histone acetyltransferase
HDAC	histone deacetylase
Hip	heat-shock-protein-70-interacting protein
HNF	hepatocyte nuclear factor
Hop	heat-shock protein organizer protein
HP1	heterochromatin-associated protein 1
HPA axis	hypothalamic/pituitary/adrenal axis
HPG axis	hypothalamic/pituitary/thyroid axis
Hr	Hairless
HRE	hormone-response element
hsp	heat-shock protein
ID	interaction domain
IR	inverted repeat
LBD	ligand-binding domain
MAPK	mitogen-activated protein kinase
MNAR	modulator of non-genomic activity of oestrogen receptor
MODY1	maturity onset diabetes of the young type 1
mPR	membrane progesterone receptor
MR	mineralocorticoid receptor
NCoR	nuclear receptor co-repressor
NGFI-B	nerve growth factor inducible factor I-B
NHR	nuclear hormone receptor
nHRE	negative hormone-response element
NR	nuclear receptor

NTD	N-terminal domain
NURD	nucleosome remodelling and histone deacetylation
NURR1	NUR-related factor 1
PAIS	partial androgen-insensitivity syndrome
P-box	proximal box
pCAF	p300/CBP-associated factor
PHA1	pseudohypoaldosteronism type 1
PI 3-kinase	phosphoinositide 3-kinase
PIC	pre-initiation complex
PLR	peroxisome-proliferator-activated receptor γ ligand resistance
PNR	photoreceptor-specific nuclear receptor
PPAR	peroxisome-proliferator-activated receptor
PPIase	peptidylprolyl isomerase
PPP1R3A	protein phosphatase 1 regulatory subunit 3A
PR	progesterone receptor
PRMT	protein arginine methyltransferase
PRTH	pituitary resistance to thyroid hormone
RAR	retinoic acid receptor
RIP140	receptor-interacting protein 140
RNA pol II	RNA polymerase II
ROR	retinoid-related orphan receptor
RTH	resistance to thyroid hormone
RXR	retenoid X receptor (9- <i>cis</i> -retinoic acid receptor)
SAP	Sin3A–Sin-associated protein
SBMA	spinobulbar muscular atrophy
SERM	selective oestrogen receptor modulator
SF1	steroidogenic factor 1
SH domain	Src homology domain
SHBG	sex-hormone-binding globulin
SHP	small heterodimer partner
SMRT	silencing mediator for retinoic acid receptor and thyroid hormone receptor
SMRTER	silencing mediator of repressed transcription
SNP	single-nucleotide polymorphism
SRC	steroid receptor co-activator
STAT	signal transducer and activator of transcription
T2DM	Type II diabetes mellitus
TAF	TATA-box-binding-protein-associated factor
TBP	TATA-box-binding protein
TF	transcription factor
TMAO	trimethylamine <i>N</i> -oxide
TPR	tetratricopeptide repeat

TR	thyroid hormone receptor
TZD	thiazolidinedione
USP	ultraspiracle
VDR	vitamin D receptor
WT	wild-type
XPR	<i>Xenopus</i> homologue of mammalian nuclear progesterone receptor