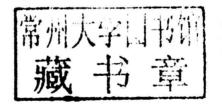


DNA METHYLATION AND COMPLEX HUMAN DISEASE

MICHEL NEIDHART University Hospital Zurich, Switzerland







Academic Press is an imprint of Elsevier 525 B Street, Suite 1800, San Diego, CA 92101-4495, USA 225 Wyman Street, Waltham, MA 02451, USA The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

Copyright © 2016 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 may 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.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-420194-1

For information on all Academic Press publications visit our website at http://store.elsevier.com

Publisher: Mica Haley

Acquisition Editor: Catherine Van Der Laan Editorial Project Manager: Lisa Eppich Production Project Manager: Melissa Read

Designer: Mark Rogers

Printed and bound in the United States of America



DNA METHYLATION AND COMPLEX HUMAN DISEASE

Preface

There is a considerable interest in whether environmental factors modulate the establishment and maintenance of epigenetic modifications, and could thereby influence gene expression and phenotype. Chemical pollutants, dietary components, temperature changes, and other external stresses can indeed have long-lasting effects on development, metabolism, and health, sometimes even in subsequent generations. The goal of this book is to provide the first comprehensive analysis of DNA methylation in human diseases, including cancer and non-neoplastic diseases. We review the possibilities of methyl groupbased epigenetic biomarkers of major diseases, tailored epigenetic therapies, and the future uses of high-throughput methylome technologies. In cancer, the distinction between mutations and epimutations becomes important in the context of possible therapeutic strategies. Thus, DNA methylation also became relevant in blood tests for non-invasive screening, and diagnostic and prognostic tests, as compared to biopsy-driven gene expression analysis. In many diseases, not only cancer, a global DNA hypomethylation is accompanied by hypermethylation of specific genes. The possibility of using methyl donors in therapeutic strategies is discussed. This book is intended for those with interests ranging from the fundamental basis of DNA methylation to therapeutic interventions. It should be a motivation for basic and applied researchers to enter this exciting and growing field.

Michel Neidhart

About the Author

Professor Michel Neidhart graduated in experimental biology in 1982, as well as nutrition and endocrinology in Montreal in 1986 and, finally, zoology at the University of Basel in 1988. After research training in Zurich and Bern, he became a researcher at the Clinic of Rheumatology at the University Hospital in Zurich (1989), senior researcher at the Center of Experimental Rheumatology (1995), and associate professor for experimental rheumatology at the Faculty of Medicine in Zurich (2009). As a researcher, Michel Neidhart has published more than 70 peer-reviewed scientific papers in the fields of endocrinology, immunology, cardiology, and rheumatic diseases.

The Center of Experimental Rheumatology has been part of the EC-supported EURO-RA Marie Curie Actions Research Training Networks (RTNs), such as EURO-RA, and was part of the EC-FP6 supported AUTOCURE project (2006–2011) and the EC FP7 MASTERSWITCH project (2008–2013). Currently the Center is supported by the Institute of Arthritis Research (2010–2016), the EC IMI BTCure (2011–2016), EC Marie Curie Osteoimmune (2012–2016), and the EC EuroTEAM (2012–2016).

androph of mode.

The second s

Contents

Preface	xiii
About the Author	XV
1. DNA Methylation – Introduction	1
 1.1 Epigenetics 1.2 Histone Modifications 1.3 DNA Methylation 1.4 Methyl-Binding Domain Proteins 1.5 DNA Demethylation 1.6 DNA Hydroxymethylation 1.7 Differentially Methylated Regions 1.8 Nutriepigenomics References 	1 2 3 4 5 5 5 6 6
2. DNA Methylation and Epigenetic Biomarkers in Cancer	9
2.1 Introduction2.2 Cancerogenesis2.3 Epimutations in Cancer2.4 ConclusionReferences	10 11 12 22 23
3. DNA Methylation and Epigenetic Biomarkers in Non-Neoplastic Diseases	29
 3.1 Introduction 3.2 Autoimmunity 3.3 Metabolic Diseases 3.4 Developmental Diseases 3.5 Psychiatric Diseases 3.6 Conclusion References 	30 30 34 36 37 38 40
4. DNA Methylation and Environmental Factors	45
4.1 Introduction4.2 Impact of the Environment in Early Life	46 46

Vi CONTENTS	
 4.3 Nutritional Factors 4.4 Adverse Environmental Factors 4.5 Immune Activation 4.6 Maternal Mood and Experience in Early Life 4.7 Physical Exercise 4.8 Conclusion References 	50 52 56 58 59 60
5 DMAN ALL STATES	at tr undi
5. DNA Methylation and Epidemiology	67
 5.1 Introduction 5.2 Endocrine Disrupting Chemicals 5.3 Epigenomics and Breast Cancer 5.4 Tobacco Smoking 5.5 Conclusion References 	67 69 71 72 75 76
6. DNA Methylation and Viral Infections	81
 6.1 Introduction 6.2 Virus Infection and Methylation Changes 6.3 Virus Infections, DNA Methylation, and Cancer 6.4 Endogenous Retroviruses 6.5 Conclusion References 	82 83 94 97 97 98
7. DNA Methylation and Cancer	103
 7.1 Introduction 7.2 Maintenance and Plasticity of the Epigenome 7.3 DNA Methylation, CpG Islands and CpG Shores 7.4 Aberrant DNA Methylation in Cancer 7.5 Epimutations, Heritable Alterations in Cancer 7.6 Epimutations of Epigenetic Regulators 7.7 Epigenetic Interplays 7.8 Reactivation of Silenced Tumor Suppressor Genes 7.9 Conclusion References 	104 105 107 111 115 119 122 126 126
8. DNA Methylation in Breast and Ovarian Carcinomas	135
8.1 Introduction8.2 Hormonal Receptors8.3 Hypomethylated Genes8.4 Hypermethylated Genes	135 136 137 138

	CONTENTS	vii
8.5 Conclusion References		152 153
9. DNA Methylation	in Acquired Drug Resistance	161
9.1 Introduction9.2 DNA Methylation and9.3 Mechanisms of Acquire9.4 ConclusionReferences		161 162 168 170 172
10. DNA Methylation	n and Endocrinology	177
10.1 Introduction 10.2 Imprinted Disorders 10.3 Rapid Promoter Meth 10.4 Exposure to Stress 10.5 Maternal and Sexual 10.6 Exposure to Endocrin 10.7 Obesity and Type 2 D 10.8 Conclusion References	e Disruptors	178 180 182 184 187 191 192 196 197
11. DNA Methylation	n in Metabolic Diseases	201
11.1 Introduction11.2 Obesity11.3 Type 2 Diabetes11.4 Epigenome-Metabolis11.5 ConclusionReferences	sm Crosstalk	201 203 205 207 210 211
12. DNA Methylation	n in Pituitary Diseases	215
12.8 Thyroid Stimulating	n Gene n Hormone inizing Hormone, Follicle Stimulating Hormone)	215 216 217 218 219 220 222 222 223 224 224

V1	11	CONTENTS

13.	DNA Methylation and Development		229
13.2 13.3 13.4 13.5 13.6 13.7	Introduction Different Embryonic Lineages Mesoderm Development Ectoderm Development Endoderm Development Hematopoietic Stem Cells Conclusion rences		229 231 235 236 237 238 238 238
14.	DNA Methylation in Growth Retardation		241
14.2 14.3 14.4 14.5 14.6 14.7 14.8 14.9	Introduction Silver-Russell Syndrome Beckwith-Wiedemann Syndrome Transient Neonatal Diabetes Mellitus Pseudohypoparathyroidism Type 1b (PHP1b) Prader-Willi and Angelman Syndromes Syndromes Mimicking Uniparental Disomy 14 (UPD14) Familial Biparental Hydratidiform Mole Conclusion rences		241 244 248 250 251 253 254 255 255
15.	DNA Methylation in Cardiology		261
15.2 15.3 15.4 15.5 15.6	Introduction Atherosclerosis Arrhythmia Ischemic Heart Disease Hypertension Conclusion rences		261 262 264 265 266 270 270
16.	DNA Methylation and Neurology		273
16.2 16.3 16.4 16.5 16.6 16.7	Introduction Co-Adaptation of Imprinted Genes Memory Alcoholism Drug Addiction Schizophrenia Conclusion rences		273 274 276 279 281 281 284 284

CONTENTS	ix
17. DNA Methylation in Psychiatric Diseases	289
17.1 Introduction	290
17.2 Major Psychosis	290
17.3 Alzheimer's Disease	293
17.4 Autism	299
17.5 Parkinson's Disease	301
17.6 Huntington's Disease	304
17.7 Amyotrophic Lateral Sclerosis	307
17.8 Conclusion	308
References	309
18. DNA Methylation in Cellular Mechanisms of	
Neurodegeneration	315
18.1 Introduction	315
18.2 Protein Misfolding	316
18.3 Protein Degradation	318
18.4 Membrane Damage	318
18.5 Mitochondrial Dysfunction	319
18.6 Axonal Transport	321
18.7 Programmed Cell Death	321
18.8 Early Life Experiences 18.9 Conclusion	322 323
References	324
References	324
19. DNA Methylation and Autoimmunity	327
19.1 Introduction	327
19.2 Environmental Factors	331
19.3 Changes in DNA Methylation	333
19.4 Conclusion	336
References	337
20. DNA Methylation in Lymphocyte Development	341
20.1 Introduction	342
20.2 Hematopoietic Cells	342
20.3 T-cell Subpopulations	343
20.4 T-cell Functions	345
20.5 B-cell Development	348
20.6 Infection and Inflammation	348
20.7 Tumor Clearance	349
20.8 Environmental Factors and Autoimmunity	350
20.9 Conclusion	352
References	353

X	CONTENTS

357
357 358 360 361 362
365 366
371
371 372 373 374 375 376 376 376 377
511
381
381 383 384 385 386 388 388 389 389
395
395 396 398 400 400 402

	CONTENTS	xi
25.	Epigenetic Therapies	405
25 1	Introduction	405
	Demethylating Agents	406
	Cancer Stem Cells – Targeted Therapies	408
	Methyl Donors	410
	Polyamine Recycling Inhibitors	412
	Conclusion	413
	rences	413
recie	Terrees	113
26.	Demethylating Agents	419
26.1	Introduction	419
26.2	Mechanism of Action	420
26.3	New Drug Development	421
26.4	Combination Therapies	422
26.5	Stem Cell Differentiation	423
26.6	Induction of Autoimmunity	423
26.7	Conclusion	424
Refe	rences	424
27.	Methyl Donors	429
27.1	Introduction	429
27.2	L-Methionine	430
27.3	Betaine	431
27.4	S-Adenosylmethionine	432
	Methionine Metabolism	432
	Polyamine Metabolism	435
	Conclusion	436
Refe	erences	436
28.	Methylome Analysis of Complex Diseases	441
28.1	Introduction	442
	Global DNA Methylation Analysis	442
	Gene-Specific Methylation Analysis	444
	Methylome-Wide Analysis	446
	Sequencing Approaches	449
	Conclusion	452
	erences	452
29.	Methylome Analysis in Cancer	457
29 1	Introduction	457

29.2 Bisulfite-Based Methods

458

xii	CONTENTS	
203	Non-Bisulfite Methods	459
	Methylated DNA Binding Column	459
	Combination with MeDiP-seq or RRBS	460
	DNA Methylation in Formalin-Fixed Paraffin-Embedded Tissues	461
	Conclusion	461
	rences	462
Title	Terroco	102
30.	Methylome Analysis in Non-Neoplastic Disease	465
30.	1 Introduction	466
30.	2 Environmental Factors	466
30.	3 Cardiovascular Diseases	469
30.	4 Inflammatory Skin Diseases	471
	5 Asthma	473
30.	6 Inflammatory Bowel Disease	473
30.	7 Rheumatic Diseases	474
30.	8 Metabolic Diseases	475
30.	9 Neurodegenerative Diseases	477
	O Psychiatric Disorders	478
	1 Neurological Disorders	480
	2 Conclusion	480
Refe	erences	481
31.	Outlook	485
Con	cluding Thoughts	485
	erences	489
IVEIG	rences	100
Glo	ossary	491
Ind	*	501
ind	lex	301