Contents

Preface XV
List of Contributors XVII

Part I General Introduction

1 The Research Program in Epigenetics: The Birth of a New Paradigm 3
Paolo Vineis
References 5

2 Interactions Between Nutrition and Health 7
Ibrahim Elmadfa
2.1 Introduction 7
2.2 Epigenetic Effects of the Diet 8
2.3 Current Nutrition Related Health Problems 8
References 9

3 Epigenetics: Comments from an Ecologist 11
Fritz Schiemer
References 12

4 Interaction of Hereditary and Epigenetic Mechanisms in the Regulation of Gene Expression 13
Thaler Roman, Eva Aumüller, Carolin Berner, and Alexander G. Haslberger
4.1 Hereditary Dispositions 13
4.2 The Epigenome 14
4.3 Epigenetic Mechanisms 15
4.3.1 Methylation 15
4.3.2 Histone Modifications 18
4.3.3 Micro RNAs 20
4.4 Environmental Influences 20
4.4.1 Nutritional and Environmental Effects in Early Life Conditions 20
4.4.2 Environmental Pollution and Toxins 22
4.5 Dietary Effects 22
### Contents

#### Part I Nutrition and Health

4.5.1 Nutrition and the Immune System 26  
4.5.2 Nutrition and Aging 26  
4.6 Inheritance and Evolutionary Aspects 28  
4.7 Conclusion 29

References 30

#### Part II Hereditary Aspects

5 Methylene tetrahydrofolate Reductase C677T and A1298C Polymorphisms and Cancer Risk: A Review of the Published Meta-Analyses 37  

*Stefania Boccia*

5.1 Key Concepts of Population-Based Genetic Association Studies 37  
5.1.1 Definition and Goals of Genetic Epidemiology 37  
5.1.2 Study Designs in Genetic Epidemiology 38  
5.1.3 The Human Genome 38  
5.1.4 Meta-Analysis in Genetic Epidemiology 39  
5.1.5 Human Genome Epidemiology Network 40  
5.1.6 “Mendelian Randomization” 41  
5.2 Methylene tetrahydrofolate Reductase Gene Polymorphisms (C677T and A1298C) and Its Association with Cancer Risk 41  
5.2.1 Gene and Function 41  
5.2.2 C677T and A1298C Gene Variants 43  
5.2.3 Gene–Environment Interaction 43  
5.3 Meta-Analyses of Methylene tetrahydrofolate Reductase C677T and A1298C Polymorphisms and Cancer 44  

References 47

6 The Role of Biobanks for the Understanding of Gene–Environment Interactions 51  

*Christian Viertler, Michaela Mayrhofer, and Kurt Zatloukal*

6.1 Background 51  
6.1.1 What Purpose Do Different Biobank Formats Serve? 52  
6.1.2 Why Do We Need Networks of Biobanks? 53  
6.2 The Investigation of Gene–Environment Interactions as a Challenge for Biobanks 55  
6.2.1 How to Evaluate Risk Factors for Metabolic Syndrome and Steatohepatitis? 58  
6.2.2 Why Are Biobanks Needed in This Context and What Challenges Do They Have to Face? 58  

References 60

7 Case Studies on Epigenetic Inheritance 63  

*Gunnar Kaati*

7.1 Introduction 64  
7.2 Methodology 65
7.2.1 On the Study of Epigenetic Inheritance 65
7.2.2 The Ideal Study Design 66
7.2.3 The Överkalix Cohorts of 1890, 1905 and 1920 67
7.2.4 The ALSPAC Data Set 68
7.2.5 The Proband’s Childhood 68
7.2.6 Food Availability 69
7.2.7 Ancestors’ Experience of Crises 69
7.2.8 Growth Velocity 69
7.3 Patterns of Transgenerational Responses 70
7.3.1 The Social Context 70
7.3.2 The Ancestors’ Nutrition 71
7.3.3 Longevity and Paternal Ancestors’ Nutrition 71
7.3.4 The Influence of Nutrition During the Slow Growth Period on Cardiovascular and Diabetes Mortality 72
7.3.5 Is Human Epigenetic Inheritance Mediated by the Sex Chromosomes? 73
7.3.5.1 Paternal Initiation of Smoking and Pregnancy Outcome 75
7.3.6 Epigenetic Inheritance, Early Life Circumstances and Longevity 75
7.3.7 How to Explain the Effects of Food Availability During SGP on Human Health? 76
7.3.7.1 Genetic Selection Through Differential Survival or Fertility? 76
7.3.7.2 Chromosomal Transmission of Nutritionally Induced Epigenetic Modifications 76
7.4 Epigenetic Inheritance 77
7.4.1 Fetal Programming and Epigenetic Inheritance 78
7.5 Future Directions 80
7.6 Conclusions 81
References 83

Part III Environmental and Toxicological Aspects

8 Genotoxic, Non-Genotoxic and Epigenetic Mechanisms in Chemical Hepatocarcinogenesis: Implications for Safety Evaluation 89
Wilfried Bursch
8.1 Introduction 90
8.2 Genotoxic and Non-Genotoxic Chemicals in Relation to the Multistage Model of Cancer Development 91
8.2.1 Tumor Initiation 91
8.2.2 Tumor Promotion 92
8.2.3 Tumor Progression 93
8.2.4 Cellular and Molecular Mechanisms of Tumor Initiation and Promotion 93
8.2.5 Epigenetic Effects of Genotoxic and Non-Genotoxic Hepatocarcinogens 96
## Contents

8.2.6 How Carcinogens Alter the Microenvironment – Crucial Roles of Inflammation 97

8.3 Concluding Remarks 97

References 99

9 Carcinogens in Foods: Occurrence, Modes of Action and Modulation of Human Risks by Genetic Factors and Dietary Constituents 105

M. Mišík, A. Nersesyan, W. Parzefall, and S. Knasmüller

9.1 Introduction 105

9.2 Genotoxic Carcinogens in Human Foods 106

9.2.1 Polycyclic Aromatic Hydrocarbons 107

9.2.2 Nitrosamines 107

9.2.3 Heterocyclic Aromatic Amines (HAAs) and Other Thermal Degradation Products 108

9.2.4 Mycotoxins 109

9.2.5 Food Additives and Carcinogens in Plant-Derived Foods 109

9.2.6 Alcohol 111

9.3 Contribution of Genotoxic Dietary Carcinogens to Human Cancer Risks 111

9.4 Protective Effects of Dietary Components Towards DNA-Reactive Carcinogens 112

9.5 Gene Polymorphisms Affecting the Metabolism of Genotoxic Carcinogens 114

9.6 Concluding Remarks, Epigenetics and Outlook 118

References 118

Part IV Nutritional Aspects

10 From Molecular Nutrition to Nutritional Systems Biology 127

Guy Vergères

10.1 Impact of Life Sciences on Molecular Nutrition Research 127

10.2 Nutrigenomics 129

10.2.1 Genomics and Nutrition Research 129

10.2.2 Transcriptomics and Nutrition Research 130

10.2.3 Proteomics and Nutrition Research 131

10.2.4 Metabolomics and Nutrition Research 132

10.3 Nutrigenetics 133

10.4 Nutri-Epigenetics 135

10.5 Nutritional Systems Biology 137

10.6 Ethics and Socio-Economics of Modern Nutrition Research 137

References 139
11 Effects of Dietary Natural Compounds on DNA Methylation Related to Cancer Chemoprevention and Anticancer Epigenetic Therapy 141
   Barbara Maria Stefanska and Krystyna Fabianowska-Majewska

   1.1 Introduction 141
   1.2 DNA Methylation Reaction 142
   1.3 Implication of the Selected Natural Compounds in DNA Methylation Regulation 144
       1.3.1 ATRA, Vitamin D3, Resveratrol, and Genistein 144
       1.3.1.1 Involvement of p21\textsuperscript{WAF1/CIP1} and Rb/E2F Pathway in Regulation of DNMT1 147
       1.3.1.2 Involvement of the AP-1 Transcriptional Complex in Regulation of DNMT1 148
       1.3.2 Polyphenols with a Catechol Group 149
   1.4 Conclusions and Future Perspectives 151

References 152

12 Health Determinants Throughout the Life Cycle 157
   Petra Rust

   1.1 Introduction 157
   1.2 Pre- and Postnatal Determinants 159
   1.3 Determinants During Infancy and Adulthood 160
   1.4 Determinants in Adults and Older People 160
   1.5 Interactions Throughout the Lifecycle 161
   1.6 Intergenerational Effects 161

References 162

Part V Case Studies

13 Viral Infections and Epigenetic Control Mechanisms 167
   Klaus R. Huber

   1.1 The Evolutionary Need for Control Mechanisms 167
   1.2 Control by RNA Silencing 168
   1.3 Viral Infections and Epigenetic Control Mechanisms 169
       1.3.1 RNA Silencing in Plants 169
       1.3.2 RNA Silencing in Fungi 170
       1.3.3 RNA Silencing in Mammals 170
   1.4 Epigenetics and Adaptive Immune Responses 171

References 171

14 Epigenetics Aspects in Gynecology and Reproductive Medicine 173
   Alexander Just and Johannes Huber

References 178
15  Epigenetics and Tumorigenesis  179
Heidrun Karlic and Franz Varga
15.1 Introduction  179
15.2 Role of Metabolism Within the Epigenetic Network  181
15.3 Epigenetic Modification by DNA Methylation During Lifetime  183
15.4 Interaction of Genetic and Epigenetic Mechanisms in Cancer  184
15.5 DNA Methylation in Normal and Cancer Cells  185
15.6 Promoter Hypermethylation in Hematopoietic Malignancies  186
15.7 Hypermethylated Gene Promoters in Solid Cancers  187
15.8 Interaction DNA Methylation and Chromatin  188
References  190

16  Epigenetic Approaches in Oncology  195
Sabine Zöchbauer-Müller and Robert M. Mader
16.1 Introduction  195
16.2 DNA Methylation, Chromatin and Transcription  196
16.3 Methods for Detecting Methylation  197
16.4 The Paradigm of Lung Cancer  198
16.4.1 Frequently Methylated Tumor Suppressor Genes and Other Cancer-Related Genes in Lung Carcinomas  199
16.4.2 Monitoring of DNA Methylation in Blood Samples  200
16.5 Epigenetics and Therapy  200
16.6 Epigenetic Alterations Under Cytotoxic Stress  201
16.7 Therapeutic Applications of Inhibitors of DNA Methylation  202
16.8 How May Methylation Become Relevant to Clinical Applications?  203
16.9 Conclusions  204
References  205

17  Epigenetic Dysregulation in Aging and Cancer  209
Despina Komninou and John P. Richie
17.1 Introduction  210
17.2 The Cancer-Prone Metabolic Phenotype of Aging  210
17.3 Age-Related Epigenetic Silencing Via DNA Methylation  212
17.4 Inflammatory Control of Age-Related Epigenetic Regulators  214
17.5 Lessons from Anti-Aging Modalities  215
17.6 Conclusions  217
References  218

18  The Impact of Genetic and Environmental Factors in Neurodegeneration:
Emerging Role of Epigenetics  225
Lucia Migliore and Fabio Coppedè
18.1 Neurodegenerative Diseases  225
18.2 The Role of Causative and Susceptibility Genes in Neurodegenerative Diseases  226
18.3 The Contribution of Environmental Factors to Neurodegenerative Diseases 231
18.4 Epigenetics, Environment and Susceptibility to Human Diseases 233
18.5 Epigenetics and Neurodegenerative Diseases 234
18.6 The Epigenetic Role of the Diet in Neurodegenerative Diseases 237
18.7 Concluding Remarks 238
References 239

19 Epigenetic Biomarkers in Neurodegenerative Disorders 245
Borut Peterlin
19.1 Introduction 245
19.2 Epigenetic Marks in Inherited Neurological and Neurodegenerative Disorders 246
19.3 Epigenetic Dysregulation in Neurodegenerative Disorders 247
19.4 Gene Candidates for Epigenetic Biomarkers 248
19.5 Conclusions 249
References 250

20 Epigenetic Mechanisms in Asthma 253
Rachel L. Miller and Julie Herbstman
20.1 Introduction 253
20.2 Epigenetic Mechanisms 255
20.3 Fetal Basis of Adult Disease 255
20.4 Fetal Basis of Asthma 256
20.5 Experimental Evidence 257
20.6 Epigenetic Mechanisms in Asthma 257
20.7 Cell-Specific Responses 259
20.8 Conclusion 259
References 260

Part VI Ways to Translate the Concept

21 Public Health Genomics – Integrating Genomics and Epigenetics into National and European Health Strategies and Policies 267
Tobias Schulte in den Bäumen and Angela Brand
21.1 Public Health and Genomics 267
21.2 The Bellagio Model of Public Health Genomics 268
21.3 The Public Health Genomics European Network 271
21.4 From Public Health Genomics to Public Health and Epigenetics/Epigenomics 272
21.5 Health in All Policies – Translating Epigenetics/Epigenomics into Policies and Practice 272
21.6 Health in All Policies as a Guiding Concept for European Policies 273
21.7 Relative Risk and Risk Regulation – A Model for the Regulation of Epigenetic Risks? 274