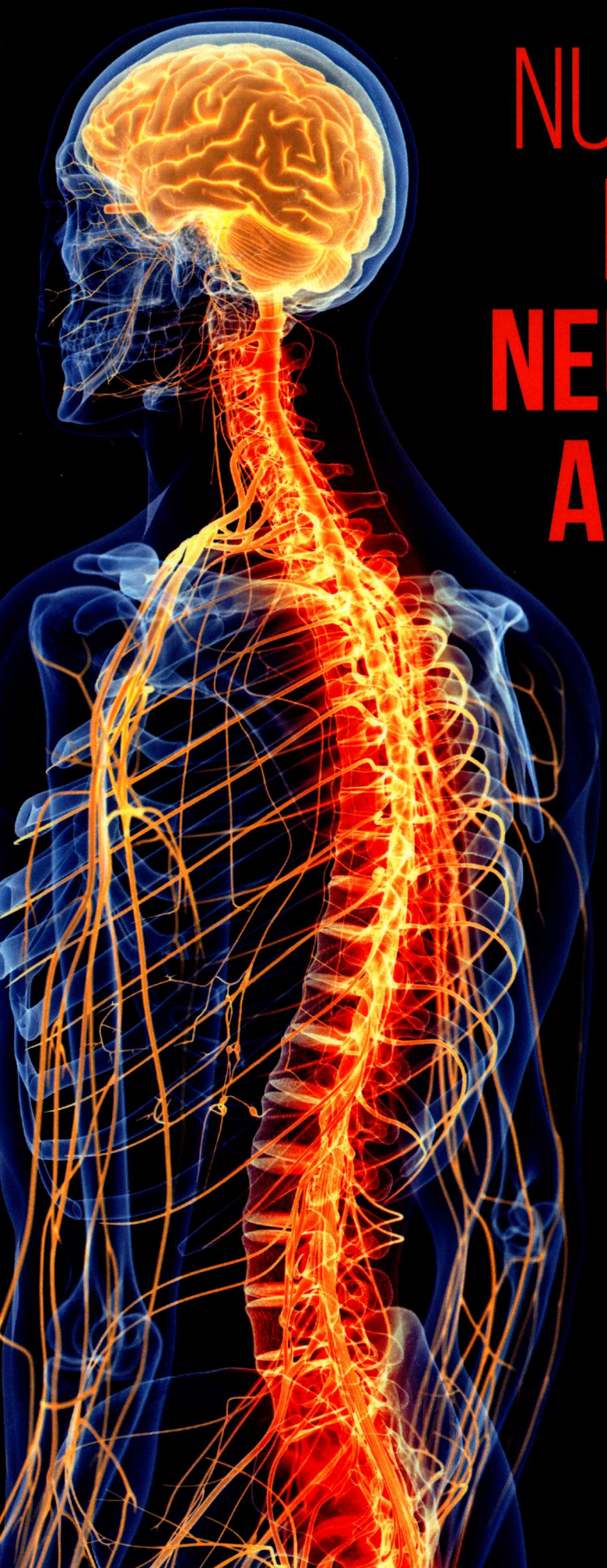
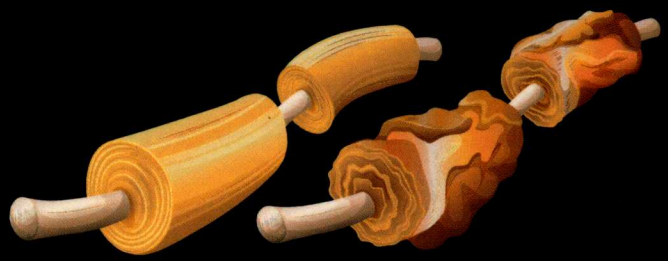


NUTRITION AND LIFESTYLE IN NEUROLOGICAL AUTOIMMUNE DISEASES: MULTIPLE SCLEROSIS



EDITED BY
RONALD ROSS WATSON
WILLIAM D. S. KILLGORE

NUTRITION AND LIFESTYLE IN NEUROLOGICAL AUTOIMMUNE DISEASES: MULTIPLE SCLEROSIS

Edited by

RONALD ROSS WATSON
University of Arizona, Arizona Health Sciences Center, Tucson, AZ, USA

WILLIAM D. S. KILLGORE
University of Arizona, College of Medicine, Department of Psychiatry, Tucson, AZ, USA

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

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

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.

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: 978-0-12-805298-3

Publisher: Mara Conner
Acquisition Editor: Melanie Tucker
Editorial Project Manager: Halima Williams
Production Project Manager: Edward Taylor
Designer: Matthew Limbert

Typeset by TNQ Books and Journals

Erratum

Watson/Nutrition and Lifestyle in Neurological Autoimmune Diseases: Multiple Sclerosis
Editors: Ronald Ross Watson and William D.S. Killgore
ISBN: 9780128052983

Page 3, copyright statement on footer should correctly read:

This chapter is a revised English translation of Neurología, M. Iridoy Zulet, L. Pulido Fontes, T. Ayuso Blanco, F. Lacruz Bescos, M. Mendioroz Iriarte, "Modificaciones epigenéticas en neurología: alteraciones en la metilación del ADN en la esclerosis multiple," Available online 12 May 2015. © 2015, with permission from La Sociedad Española de Neurología. Published by Elsevier España, S.L.U.

We apologize for this error.

NUTRITION AND LIFESTYLE IN NEUROLOGICAL AUTOIMMUNE DISEASES: MULTIPLE SCLEROSIS

List of Contributors

Y. Arima Hokkaido University, Sapporo, Japan

J.A. Armenta-Peinado University of Málaga, Málaga, Spain

L. Attorri Istituto Superiore di Sanità, Rome, Italy

F. Ayoobi Rafsanjan University of Medical Sciences, Rafsanjan, Iran

A. Barghi Harvard Medical School, Boston, MA, United States

G.S. Cantrell University of Oklahoma, Norman, OK, United States

M. Cardoso Universidade Metropolitana de Santos, Santos, SP, Brazil

A. Carter Sheffield Hallam University, United Kingdom

M.J. Casuso-Holgado University of Seville, Seville, Spain

İ. Coşkun Benlidayı Çukurova University, Adana, Turkey

C. Costantino University of Parma, Parma, Italy

R. Di Benedetto Istituto Superiore di Sanità, Rome, Italy

A. Di Biase Istituto Superiore di Sanità, Rome, Italy

A. Dixon-Ibarra Oregon State University, Corvallis, OR, United States

S. Domingo Mellen Center for Multiple Sclerosis, Cleveland, OH, United States

K. Edwards Precision Performance and Physical Therapy, Atlanta, Georgia

T. Elder Newcastle Community Fire Station, Newcastle Under Lyme, United Kingdom

J.W. Farrell University of Oklahoma, Norman, OK, United States

J. Fitzgerald Fort Lewis College, Durango, CO, United States

Y.D. Fragoso Universidade Metropolitana de Santos, Santos, SP, Brazil

R. Frank Georgia State University, Atlanta, Georgia

A.B. Gaikwad Birla Institute of Technology and Science, Pilani, Pilani, Rajasthan, India

A.E. García-Rodriguez University of Seville, Seville, Spain

M.S. Garud Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, Mumbai, India

D. Hansen Hasselt University, Diepenbeek, Belgium; Jessa Hospital, Hasselt, Belgium

C.E. Hayes University of Wisconsin–Madison, Madison, WI, United States

K. Higuchi Hokkaido University, Sapporo, Japan

L. Humphreys Sheffield Hallam University, United Kingdom

M. Iridoy Zulet Complejo Hospitalario de Navarra-IdiSNA (Navarra Institute for Health Research), Pamplona, Navarra, Spain

S.P. Kalarn University of Arizona, Tucson, AZ, United States

D. Kamimura Hokkaido University, Sapporo, Japan

J.M. Keppel Hesselink University of Witten/Herdecke, Witten, Germany

W.D.S. Killgore University of Arizona, Tucson, AZ, United States

R.E. Klaren University of Illinois at Urbana-Champaign, Urbana, IL, United States

A. Klimova University of Arizona, Tucson, AZ, United States

D.N. Krementsov University of Vermont, Burlington, VT, United States

Y.A. Kulkarni Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, Mumbai, India

D.J. Lantis University of Oklahoma, Norman, OK, United States

J. Larimore Agnes Scott College, Decatur, Georgia

R.D. Larson University of Oklahoma, Norman, OK, United States

O. Licari University of Parma, Parma, Italy

M. MacDonald Oregon State University, Corvallis, OR, United States

Sayed Mahdi Marashi Virology Department, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran

V.W. Mark University of Alabama at Birmingham, Birmingham, AL, United States

R. Martín-Valero University of Málaga, Málaga, Spain

M. Mendioroz Iriarte Complejo Hospitalario de Navarra-IdiSNA (Navarra Institute for Health Research), Pamplona, Navarra, Spain; Neuroepigenetics Laboratory, Navarrabiomed-IdiSNA (Navarra Institute for Health Research), Pamplona, Navarra, Spain

Y. Miyazaki Hokkaido Medical Center, Sapporo, Japan

A. Moghaddamahmadi Rafsanjan University of Medical Sciences, Rafsanjan, Iran

R.W. Motl School of Health Professions, Birmingham, AL, United States

M. Murakami Hokkaido University, Sapporo, Japan

M. Niino Hokkaido Medical Center, Sapporo, Japan

N. Nishikawa Hokkaido University, Sapporo, Japan

T. Ohki Hokkaido University, Sapporo, Japan

M. Orsini Centro Universitário Severino Sombra, Rio de Janeiro, Brazil; Centro Universitário Augusto Motta – UNISUAM

M.J. Oza Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, Mumbai, India; SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India

A. Palma da Cunha Matta Universidade Federal Fluminense, Rio de Janeiro, Brazil

B.A. Pribble University of Oklahoma, Norman, OK, United States

S. Rezapour-Firouzi Tabriz University of Medical Sciences, Tabriz, Iran; Urmia University of Medical Sciences, Urmia, Iran

K. Rogers Oregon State University, Corvallis, OR, United States

A. Roohbakhsh Mashhad University of Medical Sciences, Mashhad, Iran

S. Salvati Istituto Superiore di Sanità, Rome, Italy

A. Shamsizadeh Rafsanjan University of Medical Sciences, Rafsanjan, Iran

B. Sharrack Sheffield Teaching Hospital Foundation Trust, Sheffield, South Yorkshire, United Kingdom

Zabihollah Shoja Virology Department, Pasteur Institute of Iran (IPI), Tehran, Iran

P. Singh University of Arizona, Tucson, AZ, United States

A. Soundy University of Birmingham, Birmingham, United Kingdom

J.A. Spanier University of Minnesota, Minneapolis, MN, United States

A. Stofkova Hokkaido University, Sapporo, Japan

A.B. Sullivan Mellen Center for Multiple Sclerosis, Cleveland, OH, United States

E. Taub University of Alabama at Birmingham, Birmingham, AL, United States

Ronald Ross Watson University of Arizona, Tucson, AZ, United States

I. Wens Hasselt University, Diepenbeek, Belgium

Acknowledgments

The work of Dr. Watson's editorial assistant, Bethany L. Stevens, in communicating with authors and working on the manuscripts was critical to the successful completion of the book. The support of Kristi L. Anderson is also very much appreciated. Support for Ms. Stevens' and Dr. Watson's work was graciously provided by Natural Health Research Institute www.naturalhealthresearch.org. It is an independent, nonprofit organization that supports science-based research on natural health and wellness. It is committed to informing about scientific evidence on the usefulness and cost-effectiveness of diet, supplements, and a healthy lifestyle to improve health and wellness and reduce disease. Finally, the work of the librarian of the Arizona Health Science Library, Mari Stoddard, was vital and very helpful in identifying key researchers who participated in the book.

Contents

SECTION I

MECHANISMS OF MS DISEASE CAUSATION AND INTERVENTION

CHAPTER

1

Epigenetic Changes in DNA Methylation and Environment in Multiple Sclerosis

M. Iridoy Zulet[1], *M. Mendioroz Iriarte*[1,2]

[1]Complejo Hospitalario de Navarra-IdiSNA (Navarra Institute for Health Research), Pamplona, Navarra, Spain;
[2]Neuroepigenetics Laboratory, Navarrabiomed-IdiSNA (Navarra Institute for Health Research), Pamplona, Navarra, Spain

OUTLINE

INTRODUCTION

Epigenetic Regulatory Mechanisms

The first time the term epigenetics appeared in literature dates back to mid-20th century (Conrad Waddington, 1905–1975).[1] However, it has been only in the last decade that epigenetics has become one of the emerging research fields, as a promising source of knowledge, especially in medicine.

Epigenetics has been defined as the study of the mechanisms regulating gene expression without changing the sequence of deoxyribonucleic acid (DNA). This discipline has built a bridge between genetic and environmental influences on the development of a phenotype; that is, it provides the means by which genetic material can respond to the diverse environmental conditions not requiring structural changes. Epigenetic changes allow some genes to be expressed or not, depending on the external conditions, and those changes are essential in cell and tissue differentiation that occurs during embryonic development as well as in adult organisms. Thus, mammalian cells undergo epigenetic changes throughout life. In fact, identical twins with the same genetic background build different epigenetic patterns depending on the environmental factors to which they are subjected, such as smoking, diet, or exercise.[2] In addition, these epigenetics patterns cause observable differences in the phenotype of both twins, either a different behavior or different risk of disease.[3]

The main epigenetic mechanisms include DNA methylation, histone modifications, and action of noncoding RNAs. So far, DNA methylation is the best known of these mechanisms. Most studies have been focused on DNA methylation and how it is associated with the development of a disease. Therefore, our review has been focused on DNA methylation and its role in developing multiple sclerosis (MS).

Nutrition and Lifestyle in Neurological Autoimmune Diseases: Multiple Sclerosis
http://dx.doi.org/10.1016/B978-0-12-805298-3.00001-3

DNA Methylation

DNA methylation is a biochemical process by which a methyl group is added to a cytosine residue in the DNA nucleotide chain. This binding occurs in cytosine–guanine dinucleotides (CpG), which are clustered in the genome, building the CpG islands. These are especially abundant in the promoter and other regulatory regions of genes. Methylation is performed by DNA methyltransferases (DNMTs) that catalyze the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to carbon 5 of cytosine.[4] This process may be carried out following two different models: the occurrence of a "de novo" methylation pattern catalyzed by the DNMT3a and DNMT3b[5] enzymes, or by maintaining a methylation pattern in the following cycles of cell replication performed by DNMT1. The latter occurs during DNA replication. Therefore, when a CpG sequence acquires a certain methylation pattern, this modification becomes stable and is inherited as a clonal methylation pattern through subsequent cell divisions.[6]

Hypermethylation of CpG islands in the promoter region of the gene is typically a mechanism of gene repression as it inhibits transcription. This inhibition is basically performed through two processes: (1) by preventing the binding of transcription factors containing recognition sites for CpGs and (2) by means of adhering protein complexes known as methyl-binding domain (MBD) that are bound to the methylated CpG regions and block access to regulatory proteins or transcription factors.[7]

As mentioned earlier, the methyl group donor is the SAM molecule which, once it loses the methyl group, becomes S-adenosyl homocysteine (SAH). This molecule is hydrolyzed to homocysteine and then it is remethylated to methionine by 5-methyltetrahydrofolate cofactor (5mTHF). Finally, methionine is transformed back into a SAM molecule by the action of methionine adenosyltransferase (MAT). DNA methylation potential depends on the ratio between SAM level and SAH in blood. The higher the ratio, the more the methylation potential.[8] Therefore, it can be inferred that for the process of DNA methylation, proper metabolism of homocysteine and methionine is critical, as well as the metabolism of the various enzymes involved in this metabolic route and of other substances, such as folic acid and vitamin B12[9] (Fig. 1.1).

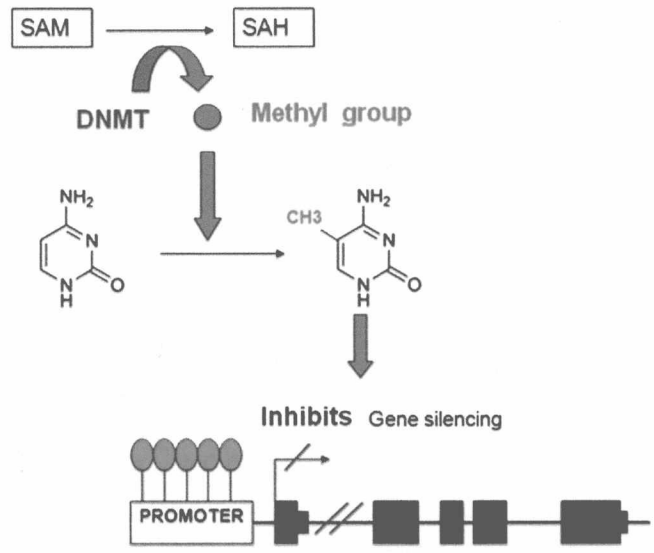


FIGURE 1.1 The process of how DNA methylation within gene promoters regulates transcription. *SAM*, S-adenosyl-L-methionine. *SAH*, S-adenosyl homocysteine. *DNMT*, DNA methyltransferases.

Relevance of DNA Methylation in Clinical Practice

Disruption of epigenetic mechanisms involved in human disease has been, for the last few years, an area of emerging research, yielding positive results in various diseases, especially in oncology. The first tumor related to mechanisms of epigenetic regulation was colorectal cancer (CRC). Initially, a loss of overall methylation was observed in cancer cells of CRC patients compared to healthy controls.[10] Also, the promoters of tumor suppressor genes were shown to be hypermethylated, which caused lower expression of those genes.[11] These findings supported that hypermethylation of tumor suppressor genes was associated with the occurrence of the disease.

However, in other areas of medicine, such as neurological disorders, how disruption of DNA methylation is involved in the disease is not well known yet. In the case of MS, epigenetic changes that might be involved in the pathogenesis of the disease have been identified, which has led to an exciting and new route of research.

MS is considered the leading cause of severe neurological disease affecting young and middle-aged adults. It is a chronic disease causing inflammatory, demyelinating, and neurodegenerative damage in the central nervous system (CNS). Its etiology is still unknown, although an autoimmune and multifactorial origin has been presumed and several genetic and environmental factors of susceptibility have been described for MS. Given the complexity of the disease and the participation of diverse, both genetic and environmental, etiological mechanisms, it is conceivable that there may be an alteration in the epigenetic regulation involved in its progression.[12,13]

RISK FACTORS IN MS AND EPIGENETIC CHANGES

Epidemiological and family aggregation studies suggest that there is a genetic predisposition for MS. However, to date, the only *locus* consistently associated with MS is the major histocompatibility complex (MHC). This predisposition has been associated with DR2