Epigenetics and Human Health 12

Luis M. Vaschetto *Editor*

Molecular Mechanisms in Nutritional Epigenetics

Springer

Epigenetics and Human Health

Volume 12

Series Editors
Rasime Kalkan, Faculty of Medicine, Department of Medical Genetics, European University of Lefke, Lefke, Northern Cyprus, Cyprus

Luis M. Vaschetto, The Ronin Institute for Independent Scholarship, Montclair, NJ, USA

This books series concerns the quickly expanding field of epigenetics. It evokes novel research questions and how these are linked to human health. Each of its volumes covers a particular topic that is important to clinical practice and research, and to researchers in epigenetics who study the relevant medical issues of today. The individual books of the series complement each other and underline the importance of epigenetics in health-related disciplines such as toxicology, reproduction, psychiatry, and nutritional and environmental medicine.

Epigenetics and Human Health is indexed in SCOPUS, EMBASE, Reaxys, EMCare, EMBiology and SCImago.

Luis M. Vaschetto
Editor

Molecular Mechanisms in Nutritional Epigenetics

Springer

Editor
Luis M. Vaschetto
The Ronin Institute for Independent Scholarship
Montclair, NJ, USA

ISSN 2191-2262 ISSN 2191-2270 (electronic)
Epigenetics and Human Health
ISBN 978-3-031-54214-5 ISBN 978-3-031-54215-2 (eBook)
https://doi.org/10.1007/978-3-031-54215-2

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2024
This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

If disposing of this product, please recycle the paper.

A mi hija María Luz

Preface

Epigenetics is the study of changes in gene expression that do not involve changes to the DNA sequence. Unlike the relatively static nature of DNA, epigenetic information systems (i.e., DNA methylation, histone modifications, and non-coding RNAs) exhibit remarkable dynamism, exerting a profound influence on our health and well-being through the modulation of gene expression. Dietary patterns influence the epigenetic landscape, ultimately determining which genes are accessible for transcription and which are silenced. In other words, nutrients can modulate our epigenome, thus impacting cellular processes, disease susceptibility, and even lifespan.

The relationship between epigenetics and nutrition plays a major role during specific developmental periods, including the prenatal and early childhood phases. Throughout these sensitive periods, the genome exhibits increased adaptability, allowing for a more robust response to environmental signals. The dietary choices made by a mother during pregnancy shape the epigenome of her growing fetus, potentially influencing their risk of developing chronic diseases, including obesity and diabetes.

Nonetheless, the epigenetic effects of nutrition extend far beyond early development, maintaining a profound influence on our health throughout the lifespan. A diet rich in specific nutrients can induce beneficial epigenetic modifications, potentially reducing disease susceptibility. In contrast, a deficient diet or excessive harmful substances can trigger detrimental epigenetic alterations, increasing the risk of developing diseases like cancer and heart disease. This understanding marks a pivotal breakthrough in personalized medicine, enabling dietary recommendation formulations specifically designed for an individual's genetic and epigenetic profile. *Molecular Mechanisms in Nutritional Epigenetics* unveils the molecular mechanisms underlying the influence of nutrition on epigenetic modifications, offering a well-documented guide to utilizing dietary strategies to enhance well-being and safeguard against diseases.

This volume of the "**Epigenetics and Human Health**" series is the fruit of a global collaboration among scientists from Argentina, Canada, China, India, Italy, Poland, Sweden, the United Arab Emirates, the United Kingdom, and the United

States of America. I sincerely wish to thank the reviewers Dr. Wellison J.S. Diniz, Prof. Gareth Davison, Dr. Anouschka Ramsteijn, Dr. Luis Vitetta, Dr. Huixin Wu, Dr. Italia Di Liegro, Dr. Jie Ren, Dr. Kara Fitzgerald, Dr. Judit Bassols, Dr. Huminska-Lisowska, Dr. Maria Vranceanu, Prof. Myron Szewczuk, Dr. Yaohua Zhang, Dr. Mahmoud Bassal, Dr. Chia-Wei Cheng, Dr. Shanel Raghubeer, Dr. Mustapha Umar Imam, Prof. Carsten Carlberg, Dr. Jyotdeep Kaur, Dr. Zahra Sepehri, Dr. Maya N. Abou Chahla, Dr. Jacob Peedicayil, and Dr. Jana Švorcova whose insightful comments have gratefully enriched the quality of this book.

Montclair, NJ, USA Luis M. Vaschetto

Contents

1 A Brief Introduction to Diet and DNA Methylation 1
Luis M. Vaschetto

2 Diet-Induced Histone Modifications: Implications for Human Health and Diseases 7
Ulfat Syed Mir, Arjamand Mushtaq, Najumu Saqib, Wajahat Waseem Tantry, and Mohammad Altaf

3 Non-Coding RNAs and Diet 31
Sushmaa Chandralekha Selvakumar, K. Auxzilia Preethi, Priya Thomas, K. P. Ameya, and Durairaj Sekar

4 Epigenetics and Nutrition: Molecular Mechanisms and Tissue Adaptation in Developmental Programming 49
Wellison J. S. Diniz, Lawrence P. Reynolds, Alison K. Ward, Joel S. Caton, Carl R. Dahlen, Kacie L. McCarthy, Ana Clara B. Menezes, Robert A. Cushman, and Matthew S. Crouse

5 Nutrition and Epigenetic Modifications During Pregnancy 71
Andrea Maugeri, Martina Barchitta, Roberta Magnano San Lio, Giuliana Favara, and Antonella Agodi

6 Nutrition, Epigenetics, and Stem Cells 105
Ahmed Taher El-Serafi and Ibrahim El-Serafi

7 Nutritional Epigenetics and Gut Microbiome 121
Abhina Mohanan, S. L. Harilal, Bhuvana Plakkot, Biju Pottakkat, and Raji Kanakkaparambil

8 Nutrition, Epigenetics, and Circadian Rhythms 161
Demin Cai, Hao-Yu Liu, Kaiqi Li, and Yanli Zhu

9 Exercise and Nutrition: Metabolic Partners in Epigenetic Regulation 183
Ciara G. Juan, Kyle B. Matchett, and Gareth W. Davison

10 Epigenetic Control and Obesity 217
Agata Chmurzynska

11 Diet, Epigenetics, and Cardiovascular Disease 237
Xuyun Liu, Xing Zhang, Jiankang Liu, and Feng Gao

12 Epigenetic Pathways from Dietary Fat to Psychopathology 263
Gillian Ragsdale

About the Editor and Contributors

About the Editor

Luis M. Vaschetto obtained his Ph.D. in Biological Sciences from the Universidad Nacional de Córdoba (Argentina). He was a postdoctoral researcher at the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and a Research Associate at the South Dakota State University (SDSU). He has been the first author of more than 10 academic articles and several book chapters. His research mainly focuses on understanding the epigenetic mechanisms involved in plant and animal development, as well as their effects on human health and diseases.

Contributors

Antonella Agodi Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Mohammad Altaf Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India

K. P. Ameya RNA Biology Lab, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India

Martina Barchitta Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Demin Cai College of Animal Science and Technology, Yangzhou University, Yangzhou, People's Republic of China

Joel S. Caton Department of Animal Sciences, and Center for Nutrition and Pregnancy, North Dakota State University, Fargo, ND, USA

Agata Chmurzynska Department of Human Nutrition and Dietetics, Poznań University of Life Sciences, Poznań, Poland

Matthew S. Crouse USDA, ARS, U.S. Meat Animal Research Center, Clay Center, NE, USA

Robert A. Cushman USDA, ARS, U.S. Meat Animal Research Center, Clay Center, NE, USA

Carl R. Dahlen Department of Animal Sciences, and Center for Nutrition and Pregnancy, North Dakota State University, Fargo, ND, USA

Gareth W. Davison Faculty of Life and Health Sciences, Ulster University, Belfast, Northern Ireland, UK

Wellison J. S. Diniz Department of Animal Sciences, Auburn University, Auburn, AL, USA

Ahmed Taher El-Serafi Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

Department of Hand Surgery and Plastic Surgery and Burns, Linköping University Hospital, Linköping, Sweden

Ibrahim El-Serafi Department of Hand Surgery and Plastic Surgery and Burns, Linköping University Hospital, Linköping, Sweden

Basic Medical Sciences Department, College of Medicine, Ajman University, Ajman, United Arab Emirates

Giuliana Favara Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Feng Gao Key Laboratory of Aerospace Medicine of Ministry of Education, School of Aerospace Medicine, Fourth Military Medical University, Xi'an, China

S. L. Harilal Department of Surgical Gastroenterology, JIPMER, Puducherry, India

Ciara G. Juan Faculty of Life and Health Sciences, Ulster University, Belfast, Northern Ireland, UK

Raji Kanakkaparambil Department of Veterinary Physiology, KVASU, Pookode, Kerala, India

Kaiqi Li College of Animal Science and Technology, Yangzhou University, Yangzhou, People's Republic of China

Hao-Yu Liu College of Animal Science and Technology, Yangzhou University, Yangzhou, People's Republic of China

Jiankang Liu Center for Mitochondrial Biology and Medicine, Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology and Department of Dermatology of the First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China

Xuyun Liu Center for Mitochondrial Biology and Medicine, Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology and Department of Dermatology of the First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China

Roberta Magnano San Lio Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Kyle B. Matchett Faculty of Life and Health Sciences, Ulster University, Belfast, Northern Ireland, UK

Andrea Maugeri Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Kacie L. McCarthy Department of Animal Science, University of Nebraska-Lincoln, Lincoln, NE, USA

Ana Clara B. Menezes Department of Animal Science, South Dakota State University, Brookings, SD, USA

Ulfat Syed Mir Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India

Abhina Mohanan Department of Surgical Gastroenterology, JIPMER, Puducherry, India

Arjamand Mushtaq Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India

Bhuvana Plakkot Department of Physiological Sciences, Oklahoma State University, Stillwater, OK, USA

Biju Pottakkat Department of Surgical Gastroenterology, JIPMER, Puducherry, India

K. Auxzilia Preethi RNA Biology Lab, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India

Gillian Ragsdale Department of Archaeology, University of Cambridge, Cambridge, UK

The Ronin Institute for Independent Scholarship, Montclair, NJ, USA

Lawrence P. Reynolds Department of Animal Sciences, and Center for Nutrition and Pregnancy, North Dakota State University, Fargo, ND, USA

Najumu Saqib Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India

Durairaj Sekar RNA Biology Lab, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India

Sushmaa Chandralekha Selvakumar RNA Biology Lab, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India

Wajahat Waseem Tantry Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India

Priya Thomas Department of Oral Pathology and Microbiology, Annoor Dental College and Hospital, Muvattupuzha, Kerala, India

Luis M. Vaschetto The Ronin Institute for Independent Scholarship, Montclair, NJ, USA

Alison K. Ward Department of Veterinary Biomedical Sciences, University of Saskatchewan, Saskatoon, SK, Canada

Xing Zhang Key Laboratory of Aerospace Medicine of Ministry of Education, School of Aerospace Medicine, Fourth Military Medical University, Xi'an, China

Yanli Zhu College of Animal Science and Technology, Yangzhou University, Yangzhou, People's Republic of China

Chapter 1
A Brief Introduction to Diet and DNA Methylation

Luis M. Vaschetto

Abstract Epigenetic regulatory mechanisms, which include DNA methylation, histone modifications, and non-coding RNA pathways, are independent of DNA sequence changes. These mechanisms, acting in concert, modulate gene expression and influence phenotypic plasticity. Environmental factors like diet can exert profound effects on epigenetic modifications, thereby affecting gene expression and cellular processes. A growing body of evidence is nowadays revealing how nutrients modify our epigenetic landscape, especially acting on DNA methylation marks to alter gene expression. This knowledge can be harnessed to develop personalized strategies, either by incorporating specific natural compounds in the diet or by using epigenetic-based therapeutic compounds, for the prevention and treatment of diseases.

Keywords DNA methylation · Diet · Gene expression · DNA methyltransferases · Phytochemicals

List of Abbreviations

CPT1A	Carnitine palmitoyltransferase-1A
DHA	Docosahexaenoic acid
DNMT	DNA methyltransferases
Fad	Fatty acid desaturase
GI	Glycemic index
SAM	S-adenosylmethionine

L. M. Vaschetto (✉)
The Ronin Institute for Independent Scholarship, Montclair, NJ, USA

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2024

L. M. Vaschetto (ed.), *Molecular Mechanisms in Nutritional Epigenetics*, Epigenetics and Human Health 12,
https://doi.org/10.1007/978-3-031-54215-2_1

1.1 Introduction

Epigenetics explores the intricate regulation of gene expression through heritable modifications that do not involve alterations in the underlying DNA sequence. Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA pathways, collaborate to modulate gene expression, reinforcing each other through intricate feedback loops. These complex epigenetic networks are fundamental during the development of multicellular organisms and underlie phenotypic plasticity in natural populations (Vaschetto 2022).

Environmental factors like exercise and diet can exert profound effects on epigenetic marks, influencing gene expression and cellular processes (see Chaps. 2 and 7 in this book). It is well-recognized that both macronutrients and micronutrients can profoundly affect DNA methylation patterns, shaping the epigenetic landscape and ultimately influencing gene expression. Numerous studies have documented the remarkable ability of dietary factors to affect DNA methylation, thereby increasing or decreasing the risk of suffering diseases such as cancer, cardiovascular disease, and metabolic and psychiatric disorders (Kulis and Esteller 2010; Skvortsova et al. 2019; also see Chaps. 10, 11, and 12 in this book). Figure 1.1 presents a simplified model overview of the relationship between dietary intake and its impact on DNA methylation patterns, ultimately influencing gene expression.

A wide spectrum of dietary factors can influence gene expression by altering DNA methylation patterns. These epigenetic pathways involve the alteration in the availability of methyl donors, the activity of DNA methyltransferases and demethylases, and the composition of the gut microbiome. Micronutrients, including vitamins and minerals, play a critical role as cofactors in DNA methylation reactions, and their deficiency can lead to DNA hypomethylation, potentially increasing the susceptibility to diseases. In contrast, macronutrients like fats may be associated with increased methylation of pro-inflammatory genes and disrupted metabolic regulation. Bioactive phytochemicals, abundant in fruits, vegetables, and herbs, can also exert epigenetic effects through their antioxidant and anti-inflammatory properties, potentially safeguarding against diseases.

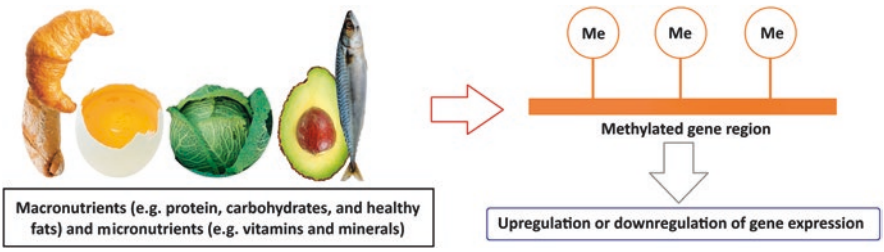

Fig. 1.1 Dietary intake modulates DNA methylation profiles at specific *loci* and leads to altered gene expression patterns

1.2 DNA Methylation and Nutrients

An appropriate dietary intake of macronutrients (i.e., carbohydrates, proteins, and lipids), vitamins (e.g., riboflavin, vitamin C, and B vitamins), and minerals (e.g., iron and calcium) is essential for persistent homeostasis due to epigenetic regulation. For example, B vitamins are critical for synthesizing S-adenosylmethionine (SAM), a key methyl group donor required for DNA methylation. Disruptions in the metabolism of these micronutrients can lead to altered DNA methylation patterns. Moreover, maternal exposure to a high-fat diet during pregnancy and lactation may modify DNA methylation patterns in the developing fetus, potentially altering gene expression and behavior in the offspring. Vander Velden and Osborne (2022) demonstrated the effect of obesity on DNA methylation and gene expression in hippocampal cells. The authors concluded that obesity interacts with aging, affecting the methylome (i.e., the complete set of DNA methylation marks in the genome) in the hippocampus, ultimately altering the expression of genes involved in neurodegeneration and metabolism.

A variety of macronutrients have been implicated in modulating DNA methylation. Noro et al. (2022) explored the associations between glycemic index (GI), a measure of how rapidly carbohydrate-rich food elevates blood sugar levels, and global DNA methylation levels. Notably, the authors observed that global DNA methylation may serve as a biomarker of carbohydrate consumption. Moreover, high-fat consumption has been associated with decreased methylation of the carnitine palmitoyltransferase-1A (*CPT1A*) gene, which may play a role in triglyceride metabolism. *CPT1A* expression has been positively correlated with triglyceride levels. Li et al. (2023) found that individuals with high DNA methylation levels in the *CPT1A* gene experienced long-term improvements in triglyceride levels when following a low-fat weight-loss diet. The consumption of amino acids, the fundamental units of proteins, can also impact DNA methylation and modulate the expression of specific traits. For instance, methionine, an essential dietary amino acid that can be supplied from different food sources (e.g., nuts, beef, cheese, fish, soy, eggs, bean, etc.), acts as a precursor for SAM through the one-carbon metabolism pathway. Studies in animals have revealed that variations in methionine consumption can alter the concentrations of SAM, resulting in changes in the expression of genes related to animal health through DNA methylation (Zhang 2018).

Micronutrients have also been associated with DNA methylation, and either their absence or excessive intake has been linked to diseased states. Fujii et al. (2019) demonstrated that high vitamin intake of vitamin A, folic acid (vitamin B9), vitamin C, vitamin D, and vitamin E is significantly associated with decreased methylation levels of the *ABCA1* gene, an ATP-binding cassette transporter involved in HDL (high-density lipoprotein)-cholesterol metabolism. On the other hand, it has been shown that increased DNA methylation levels of the promoter region in the *Hamp* gene, which encodes hepcidin, a hormone capable of negatively regulating iron homeostasis, lead to a decrease in its expression (Huang et al. 2020). In this case, altered DNA methylation may be caused by iron deficiency, which may play a role in maintaining iron homeostasis. Chang et al. (2019) suggested that a disruption in calcium intake during early development can influence the accumulation in the brain of docosahexaenoic acid (DHA) due to DNA hypermethylation of fatty acid desaturase (Fad) genes.

1.3 Dietary Factors and Modulation of DNA Methylation

The absence of essential nutrients can impair the activity of enzymes involved in the establishment of DNA methylation marks, including DNA methylases and demethylases, leading to modifications in gene expression patterns. Studies involving rat models have revealed that a folate (vitamin B-9)-deficient diet can alter the expression of key epigenetic enzymes, including the *de novo* DNA methyltransferases DNMT3a and DNMT3b and the maintenance of DNA methyltransferase DNMT1, all of them associated with gene silencing (Ghoshal et al. 2006). Moreover, Kanwal et al. (2016) demonstrated that dietary flavonoids can also modulate DNA methyltransferase activity, suggesting that flavones may confer anticancer properties by altering DNA methylation in cancer cells. Agrelius et al. (2023) explored the intricate mechanisms by which diet can induce transgenerational effects in *Daphnia*, a species that reproduces asexually. Interestingly, the authors observed that the maternal environment has a stronger influence on DNA methyltransferase gene expression when offspring had low food compared to when offspring had high food. This observation suggests that the maternal environment can influence the expression of enzymes responsible for modulating the epigenetic landscape in the offspring and that this transgenerational effect may be linked to the organism's diet.

Similarly to DNA methylation, DNA demethylation can also modify the phenotype, with a DNA demethylation state generally related to gene transcription. Deshpande et al. (2021) showed that high-fat diet-induced and genetically inherited obesity differentially alters DNA demethylase activity of germline cells in adult rats. Moreover, it has been shown that TET3, a methylcytosine dioxygenase that initiates DNA demethylation, regulates diet-induced adipogenesis by modulating the expression of target genes in adipose precursor cells (Jung et al. 2023). The authors of this study observed that decreased TET3 levels in these cells diminish adipogenesis, leading to an improvement in body metabolism. In summary, these observations suggest that organisms respond to diet by modifying gene expression through DNA methylation and demethylation; thereby modulation of the activity of these enzymes could offer a promising strategy for managing metabolic disorders like obesity.

1.4 Phytochemicals and DNA Methylation

Plant-derived compounds, known as phytochemicals, exert anticancer and disease-fighting properties by modulating DNA methylation patterns. For instance, Lee and Zhu (2006) revealed that the coffee polyphenols caffeic acid and chlorogenic acid confer concentration-dependent inhibition of DNA methylation catalyzed by the DNA methyltransferase DNMT1 in MCF-7 and MDA-MB-231 breast cancer cell lines. This inhibitory effect was attributed to the increased formation of S-adenosyl-L-homocysteine (SAH), a potent DNA methylation inhibitor. Moreover, Chatterjee et al. (2022) found that brazilin, a phytochemical found in *Caesalpinia sappan* wood, also suppresses DNMT1, decreasing global DNA

methylation in MCF-7 cells. Brazilin exerts its anticancer effects by upregulating the expression of the tumor suppressor gene *p53*. The p53 protein binds to the regulatory region in the promoter of DNMT1, reducing its transcriptional activity and ultimately restoring the expression of the cell cycle inhibitor p21 CDKN1A in MCF-7 cells.

1.5 Conclusion

The relationships between diet and DNA methylation open up promising avenues for dietary interventions to prevent or alleviate chronic diseases. Recent research has revealed how we can potentially lower disease risk and improve our overall health by tailoring dietary patterns or including dietary plant-based compounds that promote optimal gene expression patterns associated with DNA methylation/demethylation in specific cells. Future research efforts should shed light on the molecular pathways by which diet influences DNA methylation, identify specific dietary components with epigenetic regulation potential, and develop personalized nutritional strategies based on individual epigenetic profiles. Additionally, this new approach creates the possibility of developing epigenetic drugs that can increase the activity of enzymes such as DNA methylases and demethylases capable of altering the epigenetic landscape of target genes and changing the state from disease to healthy homeostasis. Further efforts need to be directed toward elucidating the full spectrum of transgenerational effects that epigenetic-based medications could induce, intending to prevent unwanted adverse events and minimizing potential transgenerational risks for future generations.Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

Ethical Approval This chapter is a review of previously published accounts; as such, no animal or human studies were performed.

References

Agrelius TC, Altman J, Dudycha JL (2023) The maternal effects of dietary restriction on Dnmt expression and reproduction in two clones of *Daphnia pulex*. Heredity 130(2):73–81. https://doi.org/10.1038/s41437-022-00581-7

Chang X et al (2019) Maternal dietary calcium status during pregnancy and lactation affects brain DHA accretion through modifying DNA methylation of fatty acid desaturases in the mouse offspring. Nutr Res 65:29–42. https://doi.org/10.1016/j.nutres.2019.01.006

Chatterjee B et al (2022) The phytochemical brazilin suppress DNMT1 expression by recruiting p53 to its promoter resulting in the epigenetic restoration of p21 in MCF7cells. Phytomedicine 95:153885. https://doi.org/10.1016/j.phymed.2021.153885

Deshpande SS, Nemani H, Balasinor NH (2021) High fat diet-induced-and genetically inherited-obesity differential alters DNA demethylation pathways in the germline of adult male rats. Reprod Biol 21(3):100532. https://doi.org/10.1016/j.repbio.2021.100532

Fujii R et al (2019) Associations between dietary vitamin intake, ABCA1 gene promoter DNA methylation, and lipid profiles in a Japanese population. Am J Clin Nutr 110(5):1213–1219. https://doi.org/10.1093/ajcn/nqz181

Ghoshal K et al (2006) A folate-and methyl-deficient diet alters the expression of DNA methyltransferases and methyl CpG binding proteins involved in epigenetic gene silencing in livers of F344 rats. J Nutr 136(6):1522–1527. https://doi.org/10.1093/jn/136.6.1522

Huang Y, Zhang H, Wang C, Zhou J, Li Y, Hu C (2020) DNA methylation suppresses liver Hamp expression in response to iron deficiency after bariatric surgery. Surg Obes Relat Dis 16(1):109–118. https://doi.org/10.1016/j.soard.2019.10.005

Jung BC, You D, Lee I, Li D, Schill RL, Ma K et al (2023) TET3 plays a critical role in white adipose development and diet-induced remodeling. Cell Rep 42(10). https://doi.org/10.1016/j.celrep.2023.113196

Kanwal R et al (2016) Dietary flavones as dual inhibitors of DNA methyltransferases and histone methyltransferases. PLoS One 11(9):e0162956. https://doi.org/10.1371/journal.pone.0162956

Kulis M, Esteller M (2010) DNA methylation and cancer. Adv Genet 70:27–56. https://doi.org/10.1016/B978-0-12-380866-0.60002-2

Lee WJ, Zhu BT (2006) Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols. Carcinogenesis 27(2):269–277. https://doi.org/10.1093/carcin/bgi206

Li X et al (2023) DNA methylation near CPT1A and changes in triglyceride-rich lipoproteins in response to weight-loss diet interventions. J Clin Endocrinol Metab:dgad086. https://doi.org/10.1210/clinem/dgad086

Noro F et al (2022) Association of nutritional glycaemic indices with global DNA methylation patterns: results from the Moli-sani cohort. Clin Epigenet 14(1):189. https://doi.org/10.1186/s13148-022-01407-3

Skvortsova K, Stirzaker C, Taberlay P (2019) The DNA methylation landscape in cancer. Essays Biochem 63(6):797–811. https://doi.org/10.1042/EBC20190037

Vander Velden JW, Osborne DM (2022) Prolonged diet-induced obesity modifies DNA methylation and gene expression in the hippocampus. Neurosci Lett 780:136656. https://doi.org/10.1016/j.neulet.2022.136656

Vaschetto LM (ed) (2022) Epigenetics, development, ecology and evolution. Springer Nature, Cham. https://doi.org/10.1007/978-3-031-13771-6

Zhang N (2018) Role of methionine on epigenetic modification of DNA methylation and gene expression in animals. Anim Nutr 4(1):11–16. https://doi.org/10.1016/j.aninu.2017.08.009

Chapter 2
Diet-Induced Histone Modifications: Implications for Human Health and Diseases

Ulfat Syed Mir, Arjamand Mushtaq, Najumu Saqib, Wajahat Waseem Tantry, and Mohammad Altaf

Abstract Post-translational modifications of histones (PTMs) are key epigenetic regulators and control chromatin-mediated processes such as gene expression, genome organization, DNA replication, and repair and recombination events. Numerous human diseases, including cancer, heart disease, autoimmune disorders, and neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease, and Huntington's disease), have been linked to misregulation of histone modifications. Histone modifications are highly dynamic and respond to various environmental cues, such as diet and dietary compounds, and have been found to alter the epigenome which impacts gene expression. In this chapter, we highlight the role of nutrition-mediated changes in epigenome and its implications for human physiology and health. A better understanding of epigenome modulation by diet may provide new ways of intervention in diseases associated with an epigenetic component and for promoting better health.

Keywords Chromatin · Epigenetics · Histone modifications · Histone methylation · Histone acetylation · Diet · Cancer

List of Abbreviations

ACTH	Adrenocorticotropic hormone
AMP	Adenosine monophosphate
BRCT domains	BRCA1 C-terminal domains

Authors "Ulfat Syed Mir" and "Arjamand Mushtaq" contributed equally to this work.

U. S. Mir · A. Mushtaq · N. Saqib · W. W. Tantry · M. Altaf (✉)
Chromatin and Epigenetics Lab, Centre for Interdisciplinary Research and Innovations, University of Kashmir, Srinagar, Jammu and Kashmir, India
e-mail: altafbhat@uok.edu.in

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2024

L. M. Vaschetto (ed.), *Molecular Mechanisms in Nutritional Epigenetics*, Epigenetics and Human Health 12,
https://doi.org/10.1007/978-3-031-54215-2_2

CBP	CREB binding protein
CPK	Calcium-dependent protein kinases
CR	Calorie restriction
CREB	Cyclic-AMP response element binding protein
DDR	DNA damage response
DHCA	Di-hydro caffeic acid
DNMT1	DNA methyltransferase 1
ECN	Erucin
EGCG	Epigallocatechin-3-gallate
ESCs	Embryonic stem cells
FAD	Flavin adenine dinucleotide
FDA	Food and Drug Administration
GTP	Green tea polyphenols
HATs	Histone acetyltransferases
HDACs	Histone deacetylases
HDMs	Histone demethylases
HR	Homologous recombination
HMTase	Histone methyltransferases
IL-6	Interleukin 6
IPA	Indole-3-propionate
JmjC	Jumonji C
KMTases	Lysine methyltransferases
Mal-gluc	Malvidin-3′-O-glucoside
MLL	Mixed lineage leukemia
NAD^+	Nicotinamide adenine dinucleotide
NHEJ	Non-homologous end joining
PCAF	p300/CBP-associated factor
PDX1	Pancreatic duodenal homeobox
POMC	β-Endorphin-producing proopiomelanocortin
PTMs	Post-translational modifications of histones
Rac1	RAS-related botulinum toxin substrate 1
ROS	Reactive oxygen species
SAM	S-adenosylmethionine
SFN	Sulforaphane

2.1 Introduction

Eukaryotic chromosomes are organized into a nucleoprotein complex called chromatin. This organization regulates all the functions of the genome. The nucleosome, the basic unit of chromatin, is made up of an octamer comprising the core histones H2A, H2B, H3, and H4 (Altaf et al. 2007; Mir et al. 2021; Mushtaq et al. 2021). Histones are basic in nature due to the presence of arginine and lysine residues which constitute around 20% of their amino acid compositions. This basic nature of histones helps them to stabilize the negatively charged DNA (Lorch et al. 2023; Cutter and Hayes

2015). Further, histones are highly conserved across species, and this conservation is responsible for the similarity in regulating cellular mechanisms from yeasts to humans (Mariño-Ramírez et al. 2006). The packaging of the eukaryotic genome into the nucleoprotein complex helps the large genome to fit within small nucleus. For instance, in mammalian cells, approximately 2 m of linear DNA must be packed into a nucleus of roughly about 10 μm diameter (Altaf et al. 2007; Mir et al. 2021; Mushtaq et al. 2021). Nucleosomes are then folded into higher order chromatin structures that eventually form a chromosome. This higher order chromatin organization not only helps in further compaction of DNA but also adds regulatory control to ensure proper gene expression (Hansen et al. 2018; Altaf et al. 2007). The compaction of the eukaryotic genome into chromatin hinders the accessibility of proteins to DNA, which are required for DNA-mediated processes, including transcription, replication, repair, and recombination (Nair et al. 2017). Therefore, chromatin structure must be dynamically regulated in order to allow access of proteins to DNA for downstream processes. The accessibility of chromatin is regulated by various factors such as DNA methylation, histone variants, nucleosome remodeling, and posttranslational modifications (PTMs) of histones (Tolsma and Hansen 2019) (Fig. 2.1). Chromatin can be broadly seen in two structurally distinguishable forms: euchromatin and heterochromatin. Euchromatin represents loosely packed, transcriptionally active, and early replicating part of the chromatin (Morrison and Thakur 2021). Euchromatin is enriched in activating histone modifications such as high levels of histone acetylation and decreased levels of repressive histone marks (e.g., H3K9/H3K27 methylation) (Morrison and Thakur 2021). Euchromatin represents a large proportion of the genome which remains localized toward the interior of nucleus. In this environment, DNA has a flexibility in terms of biological output; i.e., genes can be turned on or kept off and DNA can be untangled for repair or replication (Morrison and Thakur 2021). Heterochromatin, on the other hand, represents highly condensed, transcriptionally inactive, and late replicating part of the chromatin (Morrison and Thakur 2021). Heterochromatin is highly enriched in repressive histone marks such as H3K9 methylation and hypo-acetylated histones. Heterochromatin is present toward the periphery of the nucleus and is bound to the nuclear envelope by associating with several nuclear membrane proteins. Chromatin dynamics is modulated by various environmental signals, including diet, which influence the levels of histone modifications and change gene expression (Molina-Serrano et al. 2019). Histone modifications are considered to be the interface through which dietary interventions affect cellular phenotypes.

2.1.1 Histone Modifications

Histone proteins undergo various post-translational modifications (PTM) which mediate multiple biological processes (Ramazi et al. 2020). These modifications can alter the structure of the chromatin to either promote or suppress gene expression. Histone modifications also promote the recruitment of various proteins, thereby regulating downstream cellular functions (Chi et al. 2010). These

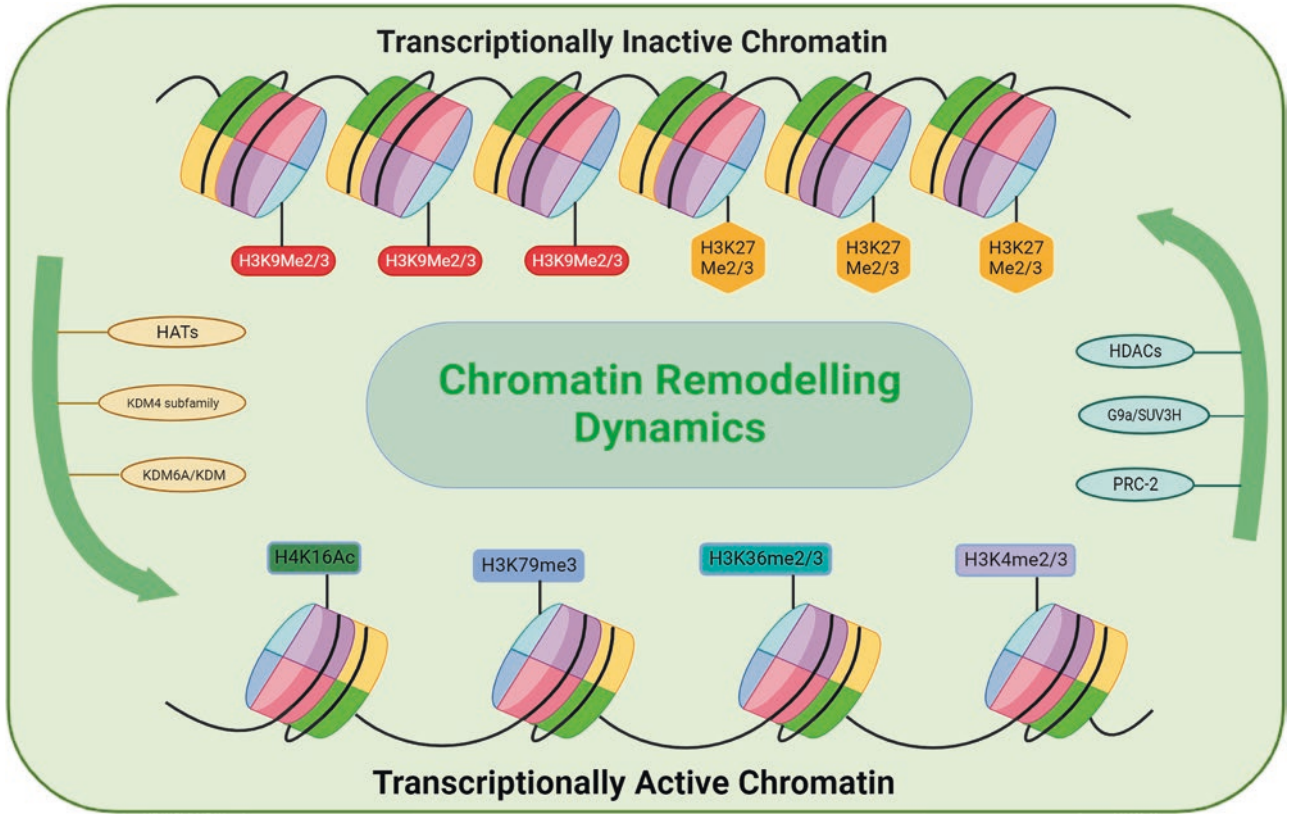

Fig. 2.1 Dynamics of chromatin remodeling by histone-modifying proteins. PRC-2, G9a/SUV39H, and HDACs are known to promote closed and transcriptionally inactive conformation of chromatin. Demethylases like KDM6A/KDM6B and KDM4 in combination with histone acetyltransferases facilitate the transcriptionally active conformation. Image created in BioRender

modifications act individually or in combination to contribute to the intricate regulation of chromatin-mediated processes (Zentner and Henikoff 2013). Various histone modifications have been reported, including acetylation, methylation, phosphorylation, and ubiquitylation (Zentner and Henikoff 2013), while others remain under investigation, such as GlcNAcylation, citrullination, crotonylation, sumoylation, and isomerization (Chen et al. 2007). N-terminal tails of histones are the main targets for post-translational modifications, although some modifications occur in the C-terminal and globular domain as well (Iwasaki et al. 2013). Histone modifications are highly dynamic, and the enzymes responsible for introducing or removing histone modifications are commonly known as "writers" and "erasers," respectively (Chi et al. 2010) (Fig. 2.1). Furthermore, the replacement of canonical histones with histone variants adds another layer of regulation to chromatin-associated processes. Incorporation of histone variants into nucleosomes alters the overall structure and accessibility of chromatin. Several histone variants have been reported, including multiple variants of histone H3, H2A, and H1, as well as at least one variant of histone H4 (Joseph and Young 2023). Histone variants undergo various post-translational modifications that regulate a diverse range of chromatin-based processes. For example, CENP-A, a histone H3 variant incorporated into centromeres, plays a critical role in chromosome segregation. CENP-A is essential for kinetochore assembly. H3.3, another histone H3 variant, is incorporated into nucleosomes independently of DNA replication and preferentially localizes to actively transcribed genes (Ng and Gurdon 2008). Histone H2A.Z, a variant of H2A, has been shown to play important roles in a variety of processes, including transcriptional activation, heterochromatin, antisilencing, DNA replication, DNA damage repair, and chromosome segregation. Additionally, H2A.Z undergoes a variety of post-translational modifications, such as acetylation, ubiquitylation, and sumoylation. These modifications alter the function of H2A.Z-containing nucleosomes (Firsanov et al. 2011; Altaf et al. 2007).

2.1.2 Histone Acetylation

Histone acetylation, one of the most well-studied histone modifications, is catalyzed by histone acetyltransferases (HATs) and reversed by histone deacetylases (HDACs) (Legube and Trouche 2003). Acetylation involves the addition of acetyl-CoA, a product of various metabolic pathways. Therefore, changes in metabolic pathways can profoundly impact gene expression through alterations in acetyl-CoA levels (Annunziato and Hansen 2000). Histone acetylation neutralizes the positive charge of lysine residues, weakening the electrostatic interaction between negatively charged DNA and otherwise positively charged histones, thereby loosening chromatin structure and making it more accessible to transcription factors (Jing et al. 2022). This can significantly increase gene expression (Roth et al. 2001). Histone acetylation is largely associated with active gene transcription. Acetylation of histones H3 and H4 inhibits the folding of chromatin into higher order compact structures and renders acetylated histone domains more accessible to proteins (Annunziato

and Hansen 2000). Histone acetylation also affects transcription elongation, as nucleosomes can block the passage of elongating RNA polymerase (Petesch and Lis 2012). Histone acetylation is also recognized as a binding site by bromodomain containing proteins present in several chromatin-associated proteins referred to as readers. In addition, PHD finger domain-containing proteins also bind to acetylated histones broadening the diversity of proteins that utilize acetylation marks to regulate various chromatin-based events (Josling et al. 2012).

2.1.3 Histone Phosphorylation

All the histone proteins in the nucleosome undergo phosphorylation at serine, threonine, and tyrosine residues (Rossetto et al. 2012). Histone phosphorylation is an important signaling cascade recognized by phospho-binding modules such as 14-3-3 and BRCT domains, which in turn regulate downstream events (Rossetto et al. 2012). Phosphorylation of the histone core plays an important role in condensation of chromosomes during cell division, regulation of transcription, and repair of damaged DNA (Altaf et al. 2007; Rossetto et al. 2012; Zhu and Wani 2010). For example, one of the early events that occurs in response to DNA damage is the phosphorylation of histone H2AX at S139 (resulting in γH2AX) that serves as binding platform for DNA damage repair proteins (Kinner et al. 2008). H2AX phosphorylation occurs in all phases of the cell cycle and regulates DNA-damage responses (DDRs) through non-homologous end joining (NHEJ), homologous recombination (HR), and replication-coupled DNA repair pathways (Firsanov et al. 2011). Phosphorylation of H2AX spans several kilobases around the break site and create binding sites for repair proteins. γH2AX has also been shown to facilitate the recruitment of histone acetyltransferases such as NuA4 that mediates chromatin modulation around the break site for efficient repair (Altaf et al. 2007; Kinner et al. 2008). Histone H3S10 phosphorylation has been extensively studied for its role in chromatin condensation during mitosis and meiosis and is used as a reference marker for these processes. Phosphorylation of H3S10 prevents H3K9 methylation and HP1 binding during M phase (Altaf et al. 2007; Komar and Juszczynski 2020).

2.1.4 Histone Methylation

Histone methylation typically occurs at lysine (K) or arginine (R) residues, using S-adenosylmethionine (SAM or AdoMet) as the methyl group donor (Hyun et al. 2017). Lysine methylation is generally more complex than other modifications, as it can occur in three states: mono- (me1), di- (me2), or trimethylation (me3) (Hyun et al. 2017). These different methylation states have been correlated with various cellular processes, including heterochromatin formation, X-chromosome inactivation, and transcriptional regulation. They have also been linked to a number of

human cancers (Klein and Costa 1997; Vallot et al. 2016). Histone lysine methylation is catalyzed by a group of enzymes called lysine methyltransferases (KMTases) that can be divided into two classes based on differences in their catalytic domain (Husmann and Gozani 2019). Members of the first KMTase class contain the evolutionary conserved SET domain and include KMT1-3 and KMT5-8 protein families, whereas the second class is formed by a single conserved non-SET protein named DOT1 (KMT4) (Dillon et al. 2005). Histone methylation was considered to be a stable mark; however, the discovery of LSD1 (lysine specific demethylase 1) that demethylates histone H3 lysine 4 showed that histone methylation is reversible like other histone modifications (Perillo et al. 2020) (Fig. 2.1).

2.2 Misregulated Histone Modifications in Cancers

Histone modifications play a critical role in regulating gene expression. A balance between histone-modifying writers and erasers is essential for maintaining cellular homeostasis (Gillette and Hill 2015). Perturbations to this balance have been implicated in various diseases, including several types of cancer (Audia and Campbell 2016). Histone H4K16 acetylation, which is associated with open chromatin decompaction, has been linked to a variety of cancers. Reduced H4K16 acetylation levels have been reported in breast cancer (Audia and Campbell 2016). Somatic mutations in histone acetyltransferases (HATs) p300 and CBP have been shown to lead to cancers in mice, with mice lacking p300 and CBP developing hematologic malignancies (Zhu et al. 2023). Chromosomal translocations that lead to hyperactivity of HATs can also cause hematological malignancies (Zhu et al. 2023). These translocations generate chimeric oncoproteins which lead to mistargeting of HATs and abnormal acetylation of specific genomic regions (Di Croce 2005; Banday et al. 2020). On the other hand, histone deacetylases are frequently overexpressed in cancers. HDCA1 has been found to be overexpressed in prostate, colon, gastric, and breast cancers (Abbas and Gupta 2008). HDAC2 is overexpressed in gastric, cervical, and colorectal cancers (Losson et al. 2016). High levels of HDAC3 and HDAC6 have been reported in colon and breast cancer tissue samples (Audia and Campbell 2016; Losson et al. 2016). Targeting histone deacetylases (HDACs) has been successful in cancer treatment. Several FDA-approved HDAC inhibitors, such as vorinostat and romidepsin, are in use for treating T-cell lymphomas, and many other HDAC inhibitors are under different phases of clinical trials (Yoon and Eom 2016). Aberrant histone methylation, like histone acetylation, has also been linked to a variety of cancers. The H3K4 methyltransferase complex MLL is frequently translocated in myeloid and lymphoid leukemias (Audia and Campbell 2016). MLL is recruited to specific genomic regions through its DNA-binding domain. In the diseased state, the MLL fusion chimeras lose their HMTase activity but retain their DNA binding ability. The translocated MLL protein fuses with a number of proteins, including AF4, AF9, AF10, and ENL (Banday et al. 2020). The chimeric proteins also interact with other epigenetic modulators, such as hDot1L, an H3K79 methyltransferase that leads to the hypermethylation of

the HOX gene cluster and promotes tumorigenesis. Inhibition of hDot1L histone methyltransferase activity suppresses the growth of MLL fusion-transformed cells and restores normal expression of the HOX gene cluster (Banday et al. 2020). This suggests that hDot1L is a driver of leukemogenesis and that its histone methyltransferase activity is essential for disease pathogenesis in mixed lineage leukemia (Banday et al. 2020). Misregulation of H3K27 methylation has also been linked to various cancers. H3K27 methylation plays important roles in many biological processes, such as genome imprinting, X-chromosome inactivation, and stem cell pluripotency (Das and Taube 2020). Aberrant expression of EZH2, the H3K27 methyltransferase, has been reported in ovarian, pancreatic, prostate, breast, kidney, gastric, and lung malignancies (Yoo and Hennighausen 2012). Alterations in the methylation of H3K9 by G9a have been reported in lung and breast cancers (Saha and Muntean 2021). Histone demethylases have also been implicated in cancer progression. Overexpression of LSD1, an H3K4 demethylase, has been reported in many cancer types. LSD1 suppresses gene expression by binding to repressive histone deacetylase complexes. Preclinical studies have shown that LSD1 inhibition suppresses lung adenocarcinoma (Perillo et al. 2020; Agboyibor et al. 2021). Given their modifiable nature, histone-modifying enzymes are emerging as attractive therapeutic targets in cancer biology. The reversibility of the epigenome has opened new avenues and represents a promising strategy for cancer chemoprevention and epigenetic-based cancer therapies.

2.3 Diet and Histone Modifications

Histones modifications are highly plastic and respond to various environmental cues. Nutrient availability and diet significantly affect the epigenome and influence gene expression (Tiffon 2018). Cells respond to dietary nutrients through signaling mechanisms which eventually lead to changes in chromatin structure to ensure appropriate gene expression (Mierziak et al. 2021) (Fig. 2.2). Histone modifications are thought to be intermediaries that link environmental signals with biological outputs. Dietary interventions such as high-fat, low-protein diets have been shown to impact multiple nutrient-sensing pathways through changes in histone modifications (Molina-Serrano et al. 2019). Several studies have reported that the quality of the maternal diet is linked to the susceptibility of offspring to metabolic disorders (Vipin et al. 2022; Harmancıoğlu and Kabaran 2023). Nutritional conditions during pregnancy can affect the epigenome, which impacts gene expression retained throughout later life (Lillycrop 2011). Several epigenetic enzymes, such as histone methyltransferases (HMTs), require cofactors that are responsive to diet for their catalytic activity (Meier 2013). For example, HMTs require S-adenosylmethionine (SAM) as a cofactor, and diet plays an important role in regulating HMT activity by providing methyl donors (Teperino et al. 2010). Moreover, the activity of histone demethylases (HDMs) is regulated by metabolic cofactors that are produced during the metabolism of high-energy nutrients (carbohydrates, proteins, or fat) (Teperino et al. 2010). There are two types of HDMs: LSD1-containing domain demethylases,

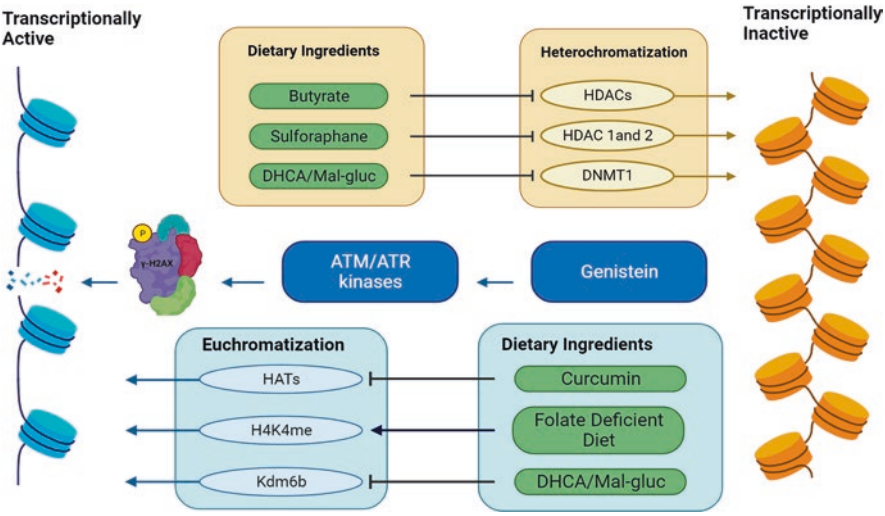

Fig. 2.2 Dietary effects on histone modifications. *Curcumin* inhibits p300/CBP HATs resulting in loss of acetylation and thus decreasing the transcription. Dietary *butyrate* is produced by the intestinal microbiota and inhibits histone deacetylases (HDACs), leading to hyperacetylation of histones and opening up the chromatin for transcription factors. *Indole-3-propionate* promotes the activity of the demethylase Kdm6b to remove H3K27me3, thus activating the transcription factor Tfam. A *folate-deficient diet* causes the enrichment of methylation as the absence of folate does not allow the activation of LSD1. Image created in BioRender

which use flavin adenine dinucleotide (FAD) as a cofactor, and Jumonji C (JmJC) domain-containing demethylases, which require α-ketoglutarate (α-KG) as a cofactor (Anand and Marmorstein 2007; Tsukada et al. 2006). The availability of extracellular nutrients can influence histone methylation by producing coenzymes through the metabolism of energy-rich molecules (Teperino et al. 2010). Dietary factors also regulate histone acetylation dynamics. Butyrate, a short-chain carboxylic acid (C4) produced by bacterial carbohydrate fermentation in the intestinal lumen, has been shown to be a potent inhibitor of class I and II HDACs (Davie 2003; Drummond et al. 2005). HDAC class III, also known as sirtuins, use NAD^+, which is synthesized from amino acids as a cofactor to deacetylate target proteins (Davie 2003; Drummond et al. 2005). The energy status of the cell is sensed by sirtuins based on the NAD^+/NADH ratio and thus facilitates the nutrition-dependent chromatin changes. During energy-rich states of the cell or hypercaloric diet intake, a low NAD^+/NADH ratio leads to decreased sirtuin activity, while caloric restriction leads to an increased NAD^+/NADH ratio and hence increased sirtuin activity (Imai et al. 2000; Vaquero and Reinberg 2009). Various dietary compounds have been reported to regulate gene expression by hyper- or hypo-acetylating histones through modulation of HDAC/HAT activity (Baur and Sinclair 2006; Kang et al. 2006). Resveratrol, a natural polyphenol obtained from red grapes and red wine, has been reported to activate SIRT1 (silent information regulator of transcription 1) and in turn prevents aging-related diseases such as osteoporosis (Lekli et al. 2010; Wu

et al. 2022). Similarly, polyphenols like epigallocatechin-3-gallate (EGCG) obtained from green tea act as histone acetyl transferase inhibitors (HAT) (Baur and Sinclair 2006; Kang et al. 2006). Thus, diet and dietary factors have a profound impact on epigenome architecture, ultimately affecting gene expression (Fig. 2.2).

2.3.1 Diet and Histone Methylation

In eukaryotes, methylation is an epigenetic modification that plays a critical role in maintaining genome integrity, genomic imprinting, transcriptional regulation, and developmental processes (Wu and Zhang 2010). Nutrition-mediated epigenomic changes can influence gene expression and our susceptibility to diseases (Bekdash 2021). Histone-modifying enzymes influence chromatin structure and topology, which is associated with changes in gene regulation (Cedar and Bergman 2009). It has been shown that diet directly affects the catalytic activities of the epigenetic writers (Wang et al. 2018). Concord grape juice, grape seed extract, and trans-resveratrol contain two phytochemical metabolic intermediates, dihydrocaffeic acid (DHCA) and malvidin-3′-O-glucoside (Mal-gluc), which attenuate depression-like behaviors in mice (Wang et al. 2018; Zhang and Kutateladze 2018). Mice treated with DHCA and Mal-gluc show increased resilience to stress and reduced depression-like behaviors. Mechanistically, DHCA reduces the expression of DNA methyltransferase 1 (DNMT1), which methylates DNA (Wang et al. 2018; Zhang and Kutateladze 2018). DNMT1-mediated methylation reduces the levels of the pro-inflammatory cytokine interleukin 6 (IL-6) genes, which have been reported to promote the development of depressive disorders (Wang et al. 2018; Zhang and Kutateladze 2018). Malvidin-3′-O-glucoside reduces the expression of histone deacetylase 2 (HDAC2), which significantly increases histone H3 acetylation at the promoter of the Rac1 (RAS-related botulinum toxin substrate 1) gene and helps reduce stress (Wang et al. 2018; Zhang and Kutateladze 2018). Low-carbohydrate ketogenic diets (LCKDs) have been shown to rescue hippocampal memory defects in a mouse model of Kabuki syndrome, which is characterized by the loss of site-specific histone methylation and defects in chromatin. In the hippocampus, LCKDs promote the formation of β-hydroxybutyrate (BHB), an HDAC inhibitor, which leads to changes in H3ac and H3K4me3 and rescues neurogenesis and memory phenotypes of Kabuki syndrome mice (Fig. 2.1) (Benjamin et al. 2017).

Nutrition is emerging as a key factor that can modulate brain plasticity and function. Poor diet during early life has been shown to increase the risk of developing mental disorders or cognitive impairments later in life (Prado and Dewey 2014; Esteban et al. 2018). Nutritional status during early life, whether good diet or malnutrition, plays an important role in shaping our response and reaction to stress during adulthood by altering the epigenome and expression of key genes in the brain (Bekdash 2021; Yam et al. 2015). S-adenosylmethionine (SAM), a universal methyl donor for DNA/histone methylation (Bekdash 2021; Goll and Bestor 2005), is a critical component in dictating cellular functions through epigenetic changes (Bekdash 2021). One-carbon metabolism, which comprises the folate and