Nilanjana Maulik · Tom Karagiannis
Editors

Molecular Mechanisms and Physiology of Disease

Implications for Epigenetics and Health

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ISBN 978-1-4939-0705-2 ISBN 978-1-4939-0706-9 (eBook)
DOI 10.1007/978-1-4939-0706-9
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014938027

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

This book is dedicated to our beloved grandmother (didibhai) for being there always for us

Nilanjana Maulik, Ph.D., F.A.H.A.

Preface

Although coined in the 1940s by Conrad Waddington and now representing an intense field of biomedical research, the precise definition of Epigenetics remains controversial. In its simplest form epigenetics refers to heritable changes that are not due to changes in the underlying DNA sequence. Whereas DNA methylation is a well-known and relatively well-characterized epigenetic mechanism, it is still debatable as to whether other processes such as histone posttranslational modifications represent epigenetics per se, given their transient nature. In this volume, we discuss DNA methylation, histone posttranslational modifications and their alteration by chromatin-modifying compounds, and regulation of gene expression by noncoding RNA and mi-RNA as part of the epigenetic umbrella. Indeed, this volume is quite broad consisting of an array of topics including epigenetic effects in various diseases such as autoimmune conditions, cardiovascular diseases, and asthma. The second part of this volume is dedicated to cancer and highlights epigenetic dysregulation in malignancy as well as a number of chapters related to emerging cancer therapeutics.

In Chap. 1, Hussain discusses epigenetic mechanisms associated with childhood diseases. Hussain provides an excellent overview of epigenetic processes in health and disease. This chapter provides a detailed overview of various childhood conditions with an epigenetic association, including various imprinting disorders, childhood malignancy, and diabetes. This is a very extensive chapter, and it highlights the broad spectrum of childhood diseases that can be linked with epigenetic perturbations. Detailed molecular and epigenetic aspects are further explored in Chap. 2 by Torano et al. in the context of neuronal differentiation. In this chapter, Torano et al. describe epigenetic processes including DNA methylation, histone posttranslational modifications, chromatin remodeling and regulation by noncoding RNA in great detail in the context of maintenance of pluripotency. They further explore how aberrant epigenetic mechanisms are associated with a myriad of neurological diseases and malignancy. Further, a detailed overview of epigenetics is provided by Westerland in Chap. 3. This chapter provides a thorough outline of the major epigenetic mechanisms and potential interventions using DNA methyltransferase inhibitors (DNMTs) and histone deacetylase inhibitors (HDACi), compounds which

are further explored in the following chapters. In a different light, regulation by modifying the histone tails by proteolytic processing is described in Chap. 4 by Mandal et al. Although not as well characterized as the other processes such as histone acetylation or methylation, as described by Mandal et al., proteolytic processing of the core histones is emerging as an important form of regulation of chromatin organization.

In Chap. 5, Turker et al. describe health implications associated with probiotics and their metabolites. This chapter focuses on anti-inflammatory effects of major probiotic metabolites which include the well-known short chain fatty acid HDACi, butyrate. In Chap. 6, Coppede and Migliore provide an excellent outline and overview of the epigenetic mechanisms associated with autoimmune diseases. Indeed, in Chap. 6 epigenetic phenomena, particularly aberrant mi-RNA processes and histone posttranslational modifications, related to major autoimmune conditions including systemic lupus erythematosus and rheumatoid arthritis are identified and described. Emerging evidence for deregulated epigenetic mechanisms associated with other autoimmune diseases such as Sjrogren's disease, psoriasis, and multiple sclerosis is also discussed in Chap. 6. Chapter 7 continues the disease-specific consideration with a discussion by Whayne, of epigenetic processes associated with cardiovascular disease. This also describes aspects of nutrition, including the well-known methyl-donor folate and tobacco use that are associated with disease. Nutritional aspects are further expanded in Chap. 8 by Burgio and Migliore, in the context of obesity and diabetes. This chapter details genetic and epigenetic mechanisms associated with metabolic syndrome, diabetes, and cardiovascular disease.

Both Chaps. 9 and 10 by Tortorella describe genetic and epigenetic mechanisms and emerging therapies associated with asthma. Traditionally, asthma has been viewed as a disease with a heritable genetic component which is exacerbated by various environmental exposures in early childhood or later in life. It is also becoming apparent that prenatal exposure can influence the risk of developing asthma in accordance with the Barker hypothesis of fetal programming (i.e., perturbations in nutritional or environmental conditions in utero lead to altered developmental programming of organs, influencing the propensity to develop the disease later in life). This idea has been investigated predominantly by exploring the use of tobacco and increased risk of developing various lung pathologies, including asthma later in life. In Chap. 9, Tortorella overviews epigenetic effects associated with prenatal and postnatal environmental exposures. Potential therapeutic avenues in the form of trefoil factor 2 (Chap. 10) and emerging nanotechnologies (Chap. 10) for managing asthma are also explored.

Although mechanisms in cancer formed parts of some of the preceding chapters, the remaining chapters are focussed entirely on the aspects of malignancy including carcinogenesis, cancer metabolism, and emerging cancer therapeutics. For example, in Chap. 11, Masih et al. describe the epigenetic effects of one-carbon metabolism and aberrant DNA methylation in cancer. In this chapter, Masih et al. provide a thorough overview of nutrients involved in one-carbon metabolism including folate, vitamins B6 and B12, choline, and betaine. This chapter also provides a

comprehensive review of the effects of these nutrients in ten common malignancies of the gastrointestinal and reproductive systems. A different aspect of aberrant metabolism, namely the Warburg effect, in cancer is the subject of Chaps. 12 and 13 by Molino et al. and Balding et al., respectively. The Warburg effect which postulates that cancer cells predominantly utilize aerobic glycolysis rather than mitochondrial respiration was first described in the 1920s. Although various small groups continued the work sporadically, it was not until the past few years that this topic is reemerging and has been recognized as a critical component of cancer biology. Although the epigenetic component of the Warburg effect is still not well characterized, there is emerging evidence for important links. Indeed, the epigenetic component of all aspects of carcinogenesis is now widely recognized, and epigenetic lesions are now not only being considered as the hallmarks of disease but also being incorporated into the multi-hit model. This is described and characterized by Migheli and Migliore in Chap. 14. Keeping on the topic of epigenetics, nutrition, and metabolism in Chap. 15, Pan et al. describe the effects of nutrition and energy intake in colon cancer. In this chapter, the key colon cancer-associated oncogenes and tumor suppressor genes are discussed in the context of tumor progression, and the cancer cell growth inhibitory effects of nutritional factors are described. Importantly, the potential prophylactic role of an anti-inflammatory diet in colon cancer is outlined.

The final three chapters in this volume deal with potential cancer therapeutics. In Chap. 16, Mazarakis describes the potential protective and therapeutic effects of dietary antioxidants and chromatin-modifying compounds in cancer. This chapter focuses on phenolic compounds from olive and HDACi from a variety of foods. Similarly, the potential of HDACi in combinatorial therapies, in this case phototherapy, is discussed in Chap. 17 by Sung. HDACi have emerged as an important new class of anticancer therapeutics with two compounds, suberoylanilide hydroxamic acid (Zolinza) and depsipeptide (Romidepsin), being approved by the FDA for the treatment of cutaneous T-cell lymphoma and more recently depsipeptide for peripheral T-cell lymphoma. It is widely accepted that the clinical utility of HDACi will predominantly involve combination with other anticancer therapeutics. In Chap. 17, the potential anticancer effects of combinations of HDACi with ultraviolet phototherapy are considered. Anticancer therapy is also the subject of Chap. 18 by Mah et al. in which, nanoparticle formulations for targeted drug delivery are described. There is much excitement regarding the potential of nanoparticles to deliver cytotoxic agents including epigenome-modifying siRNA to selectively induce apoptosis and cell-death in cancer cells. This chapter outlines varying approaches for appropriate nanoparticle preparations with potential clinical applicability.

Overall, this volume encompasses a wide range of topics related to epigenetic mechanisms in health and disease. The scope of the volume spans from descriptions of fundamental epigenetic processes to potential epigenetic interventions for preventing or treating various diseases. Epigenetic phenomena associated with numerous conditions including autoimmune diseases, cardiovascular disease,

asthma, and a variety of malignancies are detailed. Given the scope, this volume would be of appeal to a wide readership including those with interests in epigenetics and chromatin biology, disease-specific epigenetic aberrations, and emerging epigenetic-based cancer therapies.

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Acknowledgments

My deepest thanks to all the authors for their contributions. I would also like to thank my colleagues, friends, and students without whom this book would have been a distant reality. I also extend my heartfelt thanks to my husband who always encouraged and helped me to complete the book. I thank you all.

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I am eternally grateful to my friends, students, and colleagues in the Epigenomic Medicine Laboratory at the Baker IDI Heart and Diabetes Institute for their help and support. You have all made my life a bit easier. This volume is dedicated to all of you.

Tom Karagiannis, Ph.D.

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