Preface

It is not enough to discover and prove a useful truth previously unknown, but it is necessary also to be able to propagate it and get it recognized.

Jean-Baptiste Lamarck, French naturalist (1744–1829) *Philosophie Zoologique* (1809), vol. 2, p. 450

Epigenetics: a Greek term meaning "above and beyond the gene." The late Conrad Waddington, the last Renaissance evolutionary biologist from the University of Edinburgh, Scotland, coined the word *epigenetics* in the 1940s for a phenomenon: *"that phenotypes arises from genotype through programmed change."* Taking the past two decades of work on epigenetics into consideration Adrian Bird of the University of Edinburgh provided a unifying definition of epigenetics as: *"the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states."* According to Andrew Feinberg of the Johns Hopkins University, Baltimore, USA, the modern definition of epigenetics is *"information heritable during cell division other than the DNA sequence itself."* Epigenetics is one of the fundamental mechanisms that is involved in embryo development and differentiation of cell types. One of the most exciting frontiers in both epigenetics and genomics (genome sciences) is the new field of *epigenomics* which can be defined as: *"the study of epigenetic marks in a given cell type using genomics technologies."* This new discipline promises novel insights into the genome because of its potential to detect quantitative alterations, multiplex modifications, and regulatory sequences outside of genes.

Epigenomics: From Chromatin Biology to Therapeutics is mainly intended for readers in the genomics, biotechnology, and molecular medicine fields. There are quite a number of books already available covering epigenetics/epigenomics.[1] For example, the book by Jablonka and Lamb (1995) emphasizes the importance of "epigenetic inheritance and evolution" specially focusing on the Lamarckian approach, whereas the book by Allis *et al.* (2007) nicely provides the principles of epigenetics. Three recent books, by Esteller (2009), Ferguson-Smith *et al.* (2009), and Tost (2010), have covered the importance of DNA methylation in

[1] Jablonka, E., and Lamb, M. (1995) *Epigenetic Inheritance and Evolution: The Lamarckian Dimension*, New York: Oxford University Press; Allis, C. D., *et al.* (2007) *Epigenetics*, Cold Spring Harbor Laboratory Press; Esteller, M. (2009) *Epigenetics in Biology and Medicine*, Boca Raton, FL: CRC Press; Ferguson-Smith, A.C., *et al.* (2009) *Epigenomics*, New York: Springer; Tost, J. (2010) *DNA Methylation: Methods and Protocols*, New York: Springer.

development and cancer. The present book differs, in that it is the first text completely devoted to the new field of *epigenomics* covering the basic biological, biochemical, molecular, and genomics aspects of epigenetics and their importance in health and disease biology. This book focuses on the history, biology, and biochemistry of chromatin, epigenomic imprinting, assay technology platforms, and cancer biology. Particularly, this book highlights the importance of epigenomics in variation (includes polymorphism), epidemiology (environment and nutrition), and neurodegenerative diseases. The goal is to have this book serve as a reference for graduate students, post-doctoral researchers, and teachers and as an explanatory analysis for executives and scientists in biotechnology and pharmaceutical companies. Our hope is that this volume will serve as a prologue to the field for both new comers and those already active in the field. This book is differentiated from others due to its careful integration of relevant emerging chromatin immunoprecipitation (ChIP) and sequencing platforms that have been continuously used today by various scientists to decipher the code of "epi-epigenomes" in normal and diseased cells. We carefully chose the chapters written by experts in the field from academia and industry and made appropriate sections to maintain the theme expressed in the subtitle of this book: *From Chromatin Biology to Therapeutics*.

Three epigenetic systems, i.e., X-chromosome inactivation, genetic imprinting, and epigenetic modifications, are the building blocks of the field of epigenomics. *X-chromosome inactivation* is the fundamental and common type of epigenetic marking that occurs during embryogenesis in female mammals. This mechanism was experimentally demonstrated in 1961 by Mary Lyon of the Medical Research Council's Mammalian Genetics Unit in Oxfordshire, UK; thus it is referred to as *lyonization*. In 1975 Robin Holliday of the Medical Research Council's National Institute for Medical Research, London, UK, and Arthur Riggs of the Beckman Research Institute of the City of Hope, Duarte, USA independently proposed a molecular model for *somatic cell inheritance* emphasizing that DNA methylation could be an important mechanism for the control of gene expression in higher organisms.

A second form of epigenetic inheritance is *genomic imprinting*, in which "stamping" of the genetic information occurs according to whether it is inherited from the mother or the father. This has been independently shown by Azim Surani of the University of Cambridge, UK, Bruce Cattanach of the Medical Research Council's Mammalian Genetics Unit, and Davor Solter of the Max-Planck Institute for Immunobiology, Freiburg, Germany. Genomic imprinting is the prime example of "transgenerational epigenetic inheritance" because the imprint that is established in the germ-line of a parent is passed on to the offspring where it is "read" in the next generation. This discovery was a harbinger of the exciting (and currently flourishing) research area of epigenetics and epigenomics. DNA methylation, histone modifications, and nucleosome positioning are the important parts of the machinery of the epigenome. Each part involves a battery of enzymes and protein complexes, including methyltransferases, acetyl transferases, histone deactylases, and several signaling molecules. The biochemistry

of these modifications is the subject of this book. Understanding chromatin biology and the dynamics of the epigenome in development, aging, and disease states will help us to better understand the "histone code," and to develop models for screening environmental compounds and chemicals.

It is increasingly being recognized that *epigenetic modifications* are critical to disease pathogenesis. The first example of a human disease with an epigenetic mechanism was shown in cancer by Andrew Feinberg and Bert Vogelstein of the Johns Hopkins University, in 1983, but today it can be seen in several human diseases such as cardiovascular, diabetes, neurodegenerative and inflammatory diseases. Much of the recent growth in the field can be attributed to the technology-enabled ability to survey epigenetic modifications on a genome-wide scale. Large-scale epigenomic mapping projects have the potential to provide global, integrated views of different cellular states. Modern biomedical science is finally bringing together the intellectual forces of international academic researchers, industry scientists, and clinicians to map all the *methylomes* and/or *epigenomes*. Such collaborations have been initiated, and are relevant for the emerging science of epigenetics and epigenomics.

Epidemiology is the study of factors affecting the health and illness of human populations. Some of those factors include nutrition (diet), chemical exposure, behavior, and environment. It turns out that nutrition affects the way our genetic code is expressed: this was shown in the 1980s by Lars Olov Bygren of Umeå University, Sweden by analyzing agricultural records of the children growing up in Norrbotten in the nineteenth century. Effects of nurture (environment) on a species' nature (genes) were not supposed to happen so quickly and should take place over many generations and through millions of years of natural selection as proposed by evolutionary biologist Charles Darwin in his famous *On the Origin of Species*. But after all that, now Bygren and other scientists have amassed historical evidence as a trump card to play against Darwin! The present *environmental/epigenetic inheritance* principles are similar to those proposed earlier by evolutionist Jean-Baptiste Lamarck (1744–1829), who believed that the environment plays an important role in an organism's acquisition of evolutionary characteristics. Recent neo-Lamarckian researchers now believe that the environment plays a key role in a species acquiring inherited characteristics that drive variation and evolution. Decades later, many of Lamarck's theories are now being shown to be surprisingly correct.

Randy Jirtle of Duke University, Research Triangle, North Carolina, USA has shown for the first time that chemical exposure alters the physical characteristics of an organism by reducing the DNA methylation, and affects the next generations. Behavior (childhood abuse and suicidal nature) affects gene expression and passes to the next generation, as shown recently by Gustavo Turecki, a medical scientist from McGill University, Montreal, Canada. Bruno Reversade, a developmental biologist at Singapore's Institute of Medical Biology, is studying the effect of environment and genetic variant(s) on the *biology of monozygous twins*. However, no common allele or environmental factors or epigenetic factors have yet been identified behind the twinning process. In conclusion, it is now quite

evident that chemical exposures and nutrition play a significant role at the epigenetic level and affect gene expression and regulation.

Many people have contributed to making our involvement in this project possible. We thank our teachers for their excellent teaching, guidance, and mentorship, which helped us to bring about this educational enterprise. We are extremely grateful to all of the contributors to this book, without whose commitment this book would not have been possible. Many people have had a hand in the preparation of this book. Each chapter has been passed back and forth between the authors for criticism and revision; hence each chapter represents a joint composition. We thank our readers, who have made our hours putting together this volume worthwhile. We are indebted to the staff of the Cambridge University Press, and in particular Katrina Halliday for her generosity and efficiency throughout the editing of this book; she truly understands the urgency and need of this volume. We also extend our appreciation to Hans Zauner for his excellent cooperation during the development of this volume. We thank English molecular biologist Robin Holliday (presently in Australia) and Swedish epidemiologist Lars Olov Bygren, men of encyclopedic interests and knowledge, for their understanding and support in writing on historical and epidemiological aspects respectively in this book. We want to thank Professor Azim Surani, an English developmental molecular biologist, and one of the pioneers in the field of epigenetics, for his kindness in writing the Foreword to this book. Last, but not least, we thank Shyamala Appasani for her understanding and cooperation during the development of this interesting volume.

This book is the second joint project of father and son. A portion of the royalties will be contributed to the Dr. Appasani Foundation (a non-profit organization devoted to bringing social change through the education of youth in developing nations) and MINDS Foundation (**M**ental **I**llness and **N**eurological **D**iseases), which is committed to taking a grassroots approach in eliminating stigma and providing educational, financial, medical, and moral support for patients suffering from mental illness in developing countries.

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