PREFACE

This book provides new research on the patterns, functions and roles in disease of DNA methylation. Chapter One studies the disruption of DNA methylation patterns caused by exposure to environmental factors during the developmental period. Chapter Two presents transcriptional regulation by cytosine modifications through a broad concept of molecular sciences in physics, chemistry and biology, and suggests a complex network for cytosine modifications-mediated transcription depending on multiple factors. Chapter Three reviews the loss of Insulin-like growth factor 2 (IGF2) imprinting in human tumors, focusing especially on the mechanisms underlying this abnormality in epigenetic control; and summarizes recent progress on targeting this tumor specific imprinting abnormality as a novel anti-cancer approach.

Chapter 1 – DNA methylation is a critical mechanism of epigenetic gene regulation. The methylation status of CpG islands, which are GC-rich DNA regions that possess relatively high densities of CpG dinucleotide, is closely associated with gene transcription activity. Knockout studies of DNA methyltransferases, which are responsible for the methylation of cytosine residue at CpG sites, have shown that DNA methylation is essential for complete embryonic development. In the developmental period, the DNA methylation pattern derived from germ cells disappears when the fertilized egg develops into a blastocyst. The *de novo* DNA methylation pattern is then reestablished at around the stage of implantation. The global DNA methylation level also changes in the early postnatal stages. These DNA methylation processes that occur during development are associated with long-lasting phenotypic changes, including genomic imprinting, cell differentiation, and X-chromosome inactivation. This dynamic regulation of the DNA methylation status during the developmental period allows for normal development. Disruption of the DNA

methylation pattern by exposure to chemicals/metals during the developmental period is suspected to affect the development of offspring. In fact, several reports have shown that prenatal exposure to chemicals/metals causes developmental defects in the offspring through disruption of the DNA methylation status. Recently, the authors found that exposure to prenatal diesel exhaust, which contains particulate matter, disrupts the DNA methylation status of the brain of mouse offspring. In addition, it has been revealed that various environmental factors have the ability to alter DNA methylation status in the developmental stages. Further investigations will be required to elucidate the mechanism underlying the disruption of DNA methylation caused by prenatal exposure to chemicals and particulate matter and to avoid the detrimental health effects associated with aberrant DNA methylation.

Chapter 2 – Modifications at cytosine base are of great interests since they have been shown to alter during lifespan of many organisms and to involve in transcriptional regulation. The first discovered one, 5'-methylcytosine (5meC), can be converted to other modifications, 5'-hydroxymethylcytosine (5hmC), 5'-formylcytosine (5fC) and 5'-carboxycytosine (5caC) by enzymatic reactions, and the reversible conversions are also possible. This represents a model for epigenetic dynamism which is such represented by the hypothesis for active demethylation mediated by DNA repair. Some abnormalities associated with the changes in cytosine modifications suggest their importance for biological processes. Although there is a limited understanding of the biological importance of 5fC and 5caC, 5meC has been shown to associate with gene silencing, but 5hmC is commonly thought to involve in gene activation. Though this is not that simple since the effects of cytosine modifications can depend on such their genomic location, being within cytosine-guanine repeats or not, the sequence of DNA part they are included, in association with three dimensional features of DNA structure indicating how cytosine modifications affect transcriptional outcome is hard to understand. This chapter presents transcriptional regulation by cytosine modifications through a broad concept of molecular sciences in physics, chemistry and biology, and suggests a complex network for cytosine modifications-mediated transcription depending on multiple factors.

Chapter 3 – Insulin-like growth factor 2 (*IGF2*) encodes a potent fetal mitogen that regulates cell proliferation, growth, differentiation and survival. In normal tissues, the gene is maternally imprinted, and its expression is epigenetically regulated by the coordination of differential allelic DNA methylation in the imprinting control region, CTCF/SUZ12-mediated intrachromosomal looping, and allelic chromatin histone modifications in the

gene's promoters. Loss of *IGF2* imprinting has been observed in a variety of growth disorders and malignant tumors. This epigenetic mutation may provide investigators with novel biomarkers for early cancer detection, prediction, and prognosis. Targeting this tumor-specific epigenetic abnormality may represent a potential approach for the development of novel therapeutic anti-cancer strategies.