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The role of Nutraceuticals in the epigenetic settings of mRNAs and miRNAs

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***Abstract*—Both genetic alterations and epigenetic regulations of genes could lead to the development of human cancers. However, recent studies have shown that epigenetic alteration contributes signifi cantly not only to the development of cancer but also responsible for the progression of cancer to metastatic disease. The epigenetic regulations of specifi c genes in human cancer cells include DNA methylation, acetylation, histone modifi cation, nucleosome remodeling, and small non-coding RNA regulation including the regulation of microRNAs (miRNAs). Among many epigenetic regulations, DNA methylation is the most common event and has been well studied for understanding the mechanisms of epigenetic regulation of genes. The DNA hypermethylation occurs in the promoter sequences of tumor suppressor gene or tumor suppressive miRNAs leading to the down-regulation in the expression of tumor suppressor mRNAs or miRNAs, resulting in the development and progression of various cancers. Interestingly, recent studies have shown that several non- toxic natural agents known as nutraceuticals including isofl avone, curcumin, (−)-epigallocatechin-3-gallate, resveratrol, indole-3-carbinol, 3,3′-diindolylmethane, and lycopene could demethylate DNA at their hypermethylation sites or modulate histone, demonstrating their potential roles in the epigenetic regulation of mRNAs and miRNAs. These epigenetic regulations of mRNAs and miRNAs could be one of the molecular mechanisms by which nutraceuticals inhibit carcinogenesis and cancer progression, and thus either nutraceuticals or their synthetic analogs could serve as novel demethylating agents for the treatment of human malignancies.**

Keywords: DNA methylation, Acetylation, Tumor suppressor gene, Tumor suppressive miRNA.

I. INTRODUCTION

Human cancer is the second leading cause of death after cardiovascular disease in the United States and in the world. It is known that both genetic alterations and epigenetic regulations of genes could cause human cancers. The genetic changes including DNA point mutations, gene amplifi cation, gene translocation, etc. have been traditionally believed as major causes of cancer development. However, recent studies have demonstrated that epigenetic alterations contributes signifi - cantly to the development and progression of cancers [1].

Moreover, it has been found that genetic and epigenetic regulations are not separate biological events in cancer. Epigenetic regulations could cause genetic mutations while genetic mutations in epigenetic regulators could alter epigenome [1], suggesting the complex biological regulations of these genetic events in the development and progression of cancer. The epigenetic regulation of specific genes in human cancer cells include DNA methylation, histone modification, nucleosome remodeling, and small non-coding RNA (ncRNA) regulation including microRNAs (miRNAs).

These regulations lead to the alterations in the expression of genes without altering the DNA sequences. Among the different types of epigenetic regulations, DNA methylation is the most common event and has been well studied. DNA methylation is heritable and plays critical role in cell differentiation and embryogenesis. However, the hypermethylation occurs in the DNA sequences in the promoter of tumor suppressor genes which could cause gene silencing through the obstruction of transcriptional activators, leading to the development and progression of various cancers (Fig. 1).

In recent years, studies have focused on the investigations of the roles and the epigenetic regulation of miRNAs in cancer development and progression. The miRNAs could inhibit its target gene expression by binding to the 3′-untranslated region (3′-UTR) of target mRNA, causing either mRNA degradation or inhibition of translation. The miRNAs could be oncogenic