Chapter 3
Epigenetic and Cancer: An Evaluation of the Impact of Dietary Components

James A. Stokes III, Sanjay Kumar, Karyn Scissum-Gunn, Udai P. Singh, and Manoj K. Mishra

3.1 Introduction

Natural dietary compounds isolated from fruits, vegetables, and spices have shown great potential in the prevention and treatment of various diseases such as cancer [1–12]. These compounds contain several bioactive properties that are ubiquitous in plants, many of which have been used in ancient traditional medicines. Herbs, fruits, and veggies are not only a good source of fiber, vitamins and minerals, but also consist of constituents like resveratrol (RES), curcumin, genistein, polyphenols, alkaloids, phenolics and sulforaphane. Evidence indicates that these compounds may serve more than a basic nutritional function; thereby, effectively mediating the regression of multiple debilitating diseases including cancer. In addition to the compounds listed above, other polyphenols such as isothiocynates, silymarin, dialyl sulfide, lycopene, rosmarinic acid, apigenin and gingerol have demonstrated their potency against cancer [1–12]. Interestingly, these compounds have shown the ability to inhibit cancer via the facilitation of various epigenetic processes. Therefore, this chapter will focus on the epigenetic targets of these compounds, which are heavily involved in cancer prevention and therapy.

The study of epigenetics is comprehensive and includes all intracellular and extracellular interactions that may affect the expression of specific genes without directly altering nucleotide sequences [11–25]. Epigenetics can best be defined as the study of the mechanisms affecting temporal and spatial control of gene activity during the development of complex organisms [26]. Perhaps one of the best

J.A. Stokes III • S. Kumar • K. Scissum-Gunn • M.K. Mishra (✉)
Cancer Biology Research and Training Program, Department of Biological Sciences, Alabama State University, 915 S. Jackson Street, Montgomery, AL 36104, USA
e-mail: mmishra@alasu.edu

U.P. Singh
Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29208, USA

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examples of this is the epigenetic modification of chromatin during embryonic development after the fertilization of eukaryotic eggs. In fact, epigenetic changes are so wide-ranging that they can be used as molecular tools in the screening and treatment of various diseases including cancer. Cancer is the result of genetic mutations and/or epigenetic modifications stemming from the exposure to various adverse environmental factors [27–29]. Studies have shown that exposure to environmental toxins, the quality of nutrition and other factors including physical and chemical pollutants can alter gene expression and modulate individual genetic susceptibility to changes within the epigenome [17, 30]. To this end, there are several known mechanisms that are capable of altering the epigenome, which include DNA methylation, histone acetylation, chromatin remodeling and RNA-interference/interaction.

Epigenetic mechanisms often regulate the transcription of genes that facilitate cellular proliferation, differentiation, and survival. These mechanisms have also been linked with tumorigenesis. Aberrant chromatin modifications such as DNA methylation and histone acetylation are the main processes studied in cancer epigenetics [17, 31, 32]. Recent studies have demonstrated that during cancer development, approximately 50 % of all tumor suppressor genes are most likely inactivated by epigenetic rather than genetic, mechanisms [33]. Reports also suggest that bioactive dietary compounds can often restore the function of tumor suppressor genes, increase survival, and under certain circumstances induce apoptosis in many kinds of cancers [34, 35]. In addition to the transcriptional silencing of tumor suppressor genes, non-coding micro-RNAs (miRNAs) can be used to affect mRNA stability and subsequent translation by epigenetic processes during cancer progression [29, 32]. More interestingly, these miRNAs can regulate the expression of various epigenetic modifying enzymes such as methyltransferases (DNMTs), histone methyltransfereases (HMTs), and histone deacetylases (HDACs), which historically have been documented to participate in tumorigenesis [36, 37]. Recent studies also suggest that bioactive dietary compounds may target different tumor suppressor miRNAs to change the function(s) of genes that are being used to classify human cancers [38, 39]. Furthermore, miRNAs either directly or indirectly regulate cancer progression by acting as a tumor suppressor or epigenetically modifying enzyme. In a recent study, *miRNA-221* and *miRNA-222* inhibit the oncogene *KIT*, and therefore functions as a tumor suppressor in erythroblastic cells and other solid tumors of human origin [40]. Conversely, the *miRNA-29* family can directly control the expression of DNMTs and enhance the expression of both *DNMT-3a* and *DNMT-3b* causing genomic hypermethylation and the silencing of sensitive tumor suppressor genes: *FHIT* and *WWOX* [41].

3.2 Mechanism of Epigenetic: DNA Methylation

DNA methylation has been observed in many different types of organisms including mammals, plants and bacteria [42, 43]. DNA methylation occurs during DNA replication and is considered a stable gene-silencing mechanism. During this process

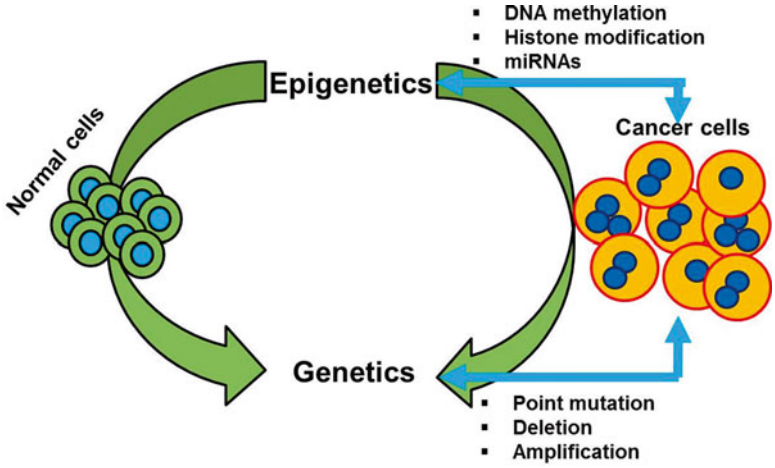

Fig. 3.1 Mutations in epigenetic modifiers not only induce cancer formation, but also induce epigenetic changes like DNA methylation, histone modification, and microRNAs, which lead to abnormal gene expression and genomic instability [52, 53]

DNMTs add methyl groups to the 5′ end of the DNA molecule, thus inactivating the affected gene by directly interfering with the assembly of transcription factors essential for gene expression. These enzymes use *S*-adneylmethionine (SAMs) to transfer methyl groups to cytosine-phosphate-guanine (CpG) sites along the DNA. However, CpG sites are not randomly distributed in the genome, but are concentrated in short CpG-rich DNA fragments commonly referred to as CpG islands [33, 44–46]. Additionally, the majority of CpG sites (except the nucleotide cytosine) are methylated, during development and differentiation in normal cells. Certain subsets of CpG islands at promoter regions may be methylated leading to long term inactivation of target genes, which can be seen in the CpG islands of tumor suppressor genes [47–51]. DNA methylation patterns are formed during cell proliferation, and can disrupt cellular division. DNA methylation is tissue specific, and distinct methylation patterns have been observed across various tissue types. Evidence indicates that the hypermethylation of genes often facilitates conditions that are conducive to carcinogenesis (Fig. 3.1) [33, 44–48, 54–59].

3.3 Histone Modification

The basic structure of the nucleosome consists of the histone octamer, which includes two molecules of each H2A, H2B, H3 and H4 proteins. The N-terminal of these proteins extends from the nucleosome core and the exposed amino acids undergo a series of covalent modifications including methylation, acetylation, phosphorylation, ubiquitinization and sumolization [11, 18, 32, 60]. Singular occurrence

or a combination of these modifying events are believed to cause inheritable epigenetic programs that facilitate different nucleosome functions such as gene transcription, the inactivation of the X-chromosome, formation of heterochromatin, mitosis and DNA repair and replication [10, 36, 57, 61, 62]. Direct interaction between the chromodomain of *Tip60* and histone H3 trimethylized on lysine 9 (H3K9me3) at double-strand breaks (DSBs) activate acetyltransferase. H3K9me3 deletion inhibits acetyltransferase activation of *Tip60*, resulting in defective ATM activation that leads to defective DSB repair. These functions are induced either by altered nucleosome interactions with chromatin or by recruiting effector proteins that possess modules that recognize specific histone modifications in a sequence specific manner. The epigenetic codes reside in the substrate specificity of the enzymes that catalyzes the various covalent modifications as well as the enzyme that reverses these modifications.

Chromatin is the template for DNA mediated processes; therefore, it might be worthy to note that histone modifications are an important component in controlling the structure and/or function of the chromatin, which often produces functional consequences. Previous reports suggest that site-specific histone modification can be linked with gene transcription [33, 63, 64]. For instance, histone H3, lysine 9 acetylation (H3K9ac), H3 serine 10 (H3S10) phosphorylation and H3 lysine 4 trimethylation (H3K4me3) are found to be associated with transcriptional activation [33, 64–67]. However, hypomethylation of H3 and H4 have shown to suppress transcription. In brief, the importance of histone modification is highlighted after the revelation that transcription apparatuses often recognize and respond to histone modifying activity [44, 58, 68]. Studies have also shown that histone H3S10 phosphorylation is catalyzed by mitogen and stress activated protein kinase 1 (MSK1). H3S10 phosphorylation is also recognized by a 14-3-3e/14-3-3y heterodimer through its interaction with H3K4 trimethyltransferase (SMYD3) and the *p52* subunit of FIIH (Fig. 3.2) [64].

3.4 microRNAs Interaction

MicroRNAs are evolutionarily conserved endogenous non-coding RNAs. MiRNAs are typically 19–25 nucleotides long, which partially or completely match the 3′ untranslated regions (3′UTR) of target RNAs. The hybridization of miRNAs to target RNAs controls gene expression by post-translational modification, silencing, and degradation mechanisms [21, 38, 40, 41, 68, 71–73]. Previous reports suggests that more than 30 % of human genes are controlled by miRNAs which suggests that these small non-coding RNAs play important roles in many biological processes including cell cycle regulation, cell growth, apoptosis, cell differentiation and stress reactions [42, 43, 74–78].

In recent studies, increased detection of miRNA among clinical samples clearly suggests that regulatory functions involve miRNAs [12, 16, 18, 21, 73, 79, 80]. According to data retrieved from the Sanger miRNA Registry in 2013, more than 800 or 1000 human miRNAs have been recorded however; many more miRNAs are

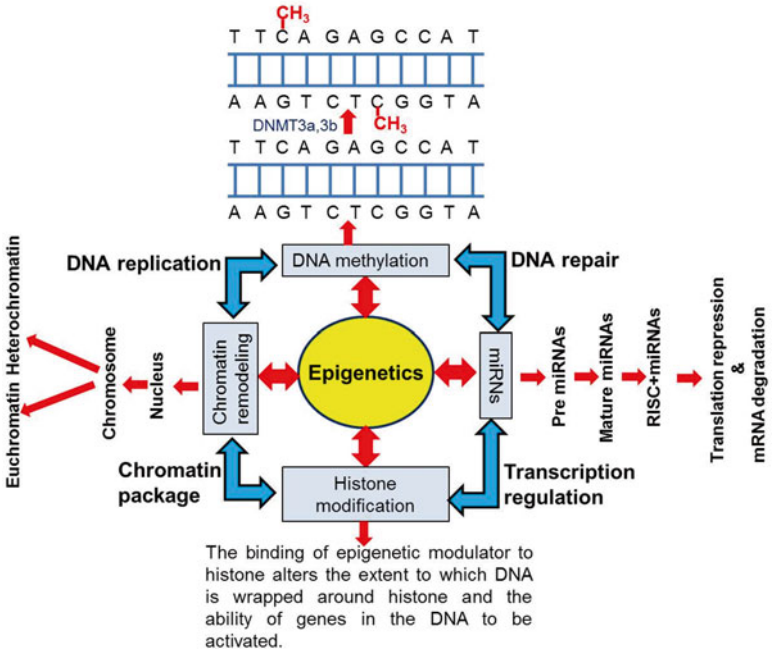

Fig. 3.2 Epigenetic mechanisms of gene regulation [69, 70]

expected to be discovered in the future [81]. miRNA control is very similar to the regulation of tightly controlled protein encoding genes. However, during cases of cancer proliferation miRNAs have been found to be greatly deregulated [42, 43, 74–78, 82–85].

Epigenetic manipulation of miRNAs is believed to be highly complex [4, 18, 21, 22, 68, 73]. Additionally, tissue specific expression of miRNAs is tightly regulated by epigenetic mechanisms such as DNA methylation and histone modification; however, miRNAs themselves can also affect epigenetic mechanisms and regulate gene transcription via post-translational gene silencing [16, 37, 41, 73]. In addition to these important biochemical pathways miRNAs can also be regulated by dietary supplements such as RES. Research shows that oncomirs such as *miR-21* are upregulated during the manifestation of various types of cancers. RES is an effective regulator of these [86–89].

3.5 Epigenetic and Carcinogenesis

Epigenetic mechanisms help to maintain cellular homeostasis during normal physiological conditions [5, 10, 13, 20, 21, 23, 24, 30, 48]. However, alterations in epigenetic regulation may lead to aberrant gene expression, which can result in the

Table 3.1 Lysine methylation pattern during cancer progression

Histone modification	Expression during cancer progression	Cancer types
H3K4me1	↑	Unknown
H3K4me2	↑	Prostate [95, 96]
H3K4me3	↓	Bladder cancer [95]
H3K9me2	↑	Gastric adenocarcinomas [95, 97]
H3K9me3	↓	Prostate [95, 97]
H3K27me3	↑	Paragangliomas [77]
H4K20me1	↓	Bladder cancer, Lymphomas, colorectal adenocarcinomas [77, 78], breast carcinomas, bladder cancer, liver cancer, non-small cell lung cancer
H4K20me3	↓	Lymphomas, colorectal adenocarcinomas [77, 78], breast carcinomas, bladder cancer, liver cancer, non-small cell lung cancer

development of cancer. Cancer development is typically associated with genetic mutation and the subsequent improper unregulated functioning of genes [9, 15, 40, 44, 54, 90–94]. However, our understanding shows that carcinogenesis cannot be the result of genetic alterations alone, but also involve epigenetic changes such as DNA methylation, histone modifications and microRNAs (Fig. 3.2). The level of lysine methylation varies and depends upon cell type. Data suggests that these molecular changes are associated with different types of cancers (Table 3.1).

Additionally, the deregulation of lysine methyltransferase and demethylases has been found in a variety of cancers as shown in Tables 3.2 and 3.3.

These changes lead to stable alterations in the pattern of gene expression that control the neoplastic phenotype, such as cellular growth and invasiveness. At this point, we focused on epigenetic targets of the bioactive compound resveratrol (RES) and its role in cancer prevention and therapy.

RES is a dietary polyphenol obtained from grapes, berries, peanuts, and other plant sources. RES shows a wide range of anti-cancer benefits such as modulating signal transduction pathways that regulate growth, differentiation, apoptosis, inflammation, angiogenesis, and metastasis [117–122]. Studies also suggest that treatment with RES inhibits the proliferation of various human cancers such as skin, breast, prostate, lung and colon [123–127]. The success of RES has led to the development of preclinical animal studies in an effort to determine the potential of this agent for cancer chemotherapeutics. Furthermore, RES has shown remarkable effects against cancer cells at both the biochemical and molecular levels [128].

RES has weaker DNMT inhibitory activity as compared to other bioactive compounds such as epigallocatechin-3-gallate (EGCG). In addition, RES inhibits epigenetic silencing of *BRCA-1* induced by aromatic hydrogen receptor (AhR) in MCF-7 cells [129]. Studies show that treatment with RES results in AhR-mediated enrichment of mono-methylated-H3K9, DNMT1, and methyl-binding domain protein-2 at the *BRCA-1* promoter, which was associated with *BRCA-1* reactivation in MCF-7 cells [129]. Conversely, it has also been reported that RES induces retinoic

Table 3.2 Histone lysine methyltransferases implications in cancer

Histone modifier	Changes during cancer	Cancer types
MLL1	Translocation, amplification, duplication	Human lymphoid and myloid leukemia [98, 99]
MENIN	Mutated	Multiple endocrine neoplastia type-1 [94, 100]
Ash2L	Increase expression	Squamous cell carcinoma of cervix and lyrix, melanoma, rhabdomyosarcoma, breast and colon carcinoma, pancreatic ductal adenocarcinoma and gastric carcinoma [101, 102]
	Low level	Hepatocellular carcinoma [103]
Ezh2	Over expression	Prostate neuroblastoma, breast cancer [51, 104]
	Mutation	B cell lymphoma, gallbladder adenocarcinoma [105]
Suv39H1	Over expression	Colon
SMYD3	Over expression	Colon, breast, hepatocellular carcinoma [105]
RIZ1	Mutation/down regulation	Liver breast and gastric cancer [105]
NSD1	Translocation	acute myeloid leukemia [14, 106]
	Mutation	Soto's syndrome [14]
	Silencing by promotor	Neuroblastoma and gliomas
	Hyper mutation	
NSD2	Translocation	Multiple myeloma
	Over expression	Multiple tumors
NSD3	Translocation	Leukaemia
	Amplification	Breast cancer [107, 108]
G9a	Over expression	Hepatocellular carcinoma [107, 108]
	Hypoxia mediated upregulation	Gastric, lung cancer [109]

Table 3.3 Histone lysine demethylase implicated in cancer

Histone activator	Changes during cancer	Cancer types
LSD1	Over expression	Prostate, neuroblastoma, breast cancer [67, 110]
	Low level	Hepatocellular carcinoma [67, 110]
FBXL10	Mutation	Lymphoma [111]
	Decrease	Brain glioblastoma
JMJD2C	Over expression	Prostate, oesophageal squamous cell carcinoma, desmoplastic medulloblastoma, MALT lymphoma [103, 111–113]
RBP2	Over expression	Gastric cancer [114]
PLU-1	Over expression	Breast, prostate, testis, ovary, lung, bladder cancer [115]
UTX	Mutations	Multiple myeloma, renal cell carcinoma [116]
JMJD3	Over expression	Prostate, pancreatic cancer, lymphoma [116]

acid receptor beta 2 (RARbeta2) expressions by blocking RARbeta2 promoter methylation in MCF-7 cells as compared to other adenosine analogs [130]. Furthermore, RES induced activation of the type III HDAC inhibitors, *sitrin 1* (*SIRT1*) and *p300*, in several *in vitro* and *in vivo* models [131]. However, activated *SIRT1* negatively down regulated the expression of survivin by deacetylase activity [132–135]. Human *BRCA-1* breast cancer cells showed decrease expression of *SIRT1* [132–135]. RES has been shown to induce the activation of *SIRT1* by altering H3 acetylation. This proved to be a useful approach for target therapy for *BRCA-1* mediated breast cancer [136]. Furthermore, *SIRT1* associated *BRCA1* signaling is important for targeting tumorigenesis by activating oncoproteins in human breast cancer [136]. It has been shown that *SIRT1*-encoded proteins are needed for RES-induced chemotherapy in APC/+ and APC/− mice [137]. *SIRT1* also play an important role in aging, since *SIRT1* null mice are unable to tolerate caloric restriction and fail to extend their life duration [137]. This demonstrates RES's ability to modulate epigenetic processes via the activation of expressed HDAC inhibitors [138].

3.6 Conclusion and Future Prospects

The emerging field that involves nutritional genomics to target nutrient related genetic and epigenetic alterations for cancer therapeutics is unique and timely. The bioactive dietary compound (RES) holds great potential not only in the prevention, but also in the therapy of a wide range of cancers by inducing epigenetic modifications. Cancer is a highly resistant disease and uses several survival pathways to prevail over normal cells. RES can act at several levels to inhibit multiple cellular pathways (for instance the induction of *SIRT1* and the inhibition of NFkB) and can be developed as a potential therapeutic agent. Many bioactive dietary compounds have shown great promise in targeting many cellular pathways involved in carcinogenesis as compared to other traditional therapies. However, further research is needed to assess organ specificity, bioavailability and general safety of these dietary compounds for any prudent conclusions. Empirical evidence of the healing powers of ancient medicines strongly supports the use of RES for cancer therapy.

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