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Transforming Cancer Epigenetics Using Nutritive Approaches and Non-coding RNAs

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Abstract

Cancer is considered one of the leading causes of death in the United States. Although preventive strategies, early detection, and improved treatment options have been developed, novel targets and therapeutics are still needed. Since concluding that cancer is mediated by genetic and epigenetic alterations of the cell, many research groups are now focusing on other means of prevention and therapy via nutrition, epigenetic mechanisms, and non-coding RNAs which have been shown to control gene expression and have many different functions at the cellular level. With the advent of high-throughput sequencing in human cancer, the potential to identify novel biomarkers and therapeutic targets of disease has increased tremendously and led to the identification of many non-coding RNAs that are dysregulated in various cancers. Gene expression and regulation is important in maintaining the homeostasis of normal tissues and cells. Not uncommonly, up- or down-regulation of particular genes are associated with cancer as a result of increased or decreased expression of transcriptional targets. This review focuses on the role of nutrition in cancer and the dysregulation of non-coding RNAs with particular emphasis on long non-coding RNAs and microRNAs in different cancer types.

Keywords

Cancer; epigenetics; non-coding RNA; nutrition; prevention; targets; therapy

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CONFLICT OF INTEREST

The authors declare that they have no financial conflict of interest.

INTRODUCTION

Cancer is a worldwide problem dating back as early as 2500 B.C. that was said to have “no treatment” [1, 2]. Although significant progress has been made with respect to the derivation of cancer, identification of carcinogens, determination of the link between viruses and cancer in humans [3] and improved treatments that often lead to complete remission, it is still one of the leading causes of death in the United States with the number of new cases expected to rise by approximately 70% over the next 20 years [4]. Current treatment options include surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, immunotherapy, and stem cell transplant [5]. Typically, cancer treatments are based on the best treatment available for the type of cancer that the patient has, as well as other factors, including risks and benefits of the treatment and the patient’s age; however, the majority of cancer treatment options pose nutrition risk which could lead to malnutrition and affect overall patient outcome, consequently leading to decreased or ineffective treatment. Despite ongoing research and the many technological advancements that have been made, there is still a great need for prevention and treatment options that are less toxic, more cost-effective and potentially nutritionally advantageous.

Some cancers are preventable with the appropriate balance of physical activity and nutrition [6]. Several studies have shown that biologically active components of some fruits and vegetables may have a promising protective effect against cancer cell formation and proliferation. The mechanism of action has yet to be fully determined, but it has been suggested that alterations in epigenetic mechanisms may have a vital role in this phenomenon [7]. The emergence of epigenetics and the correlation that has been found between factors such as diet and lifestyle with various cancers emphasizes that proper nutrition is critical during all phases of life. Elucidating the influence of nutritional involvement in epigenetic mechanisms may be instrumental in predicting inter-individual differences with respect to susceptibility to cancer and providing uses of natural compounds against cancer [8, 9]. The purpose of this review is to provide an overview of current research on cancer epigenetics and nutrition and to elaborate the potential of non-coding RNAs (ncRNAs) and dietary factors in cancer prevention and therapy.

NUTRITION IN CANCER AND EPIGENETICS

Nutrition is the process of consuming nutrients, substances that the body uses for normal functions such as growth, maintenance, repair, and digestion from the foods that are consumed. It has been revealed that nutrients affect gene expression and development of various proteins that are essential in the formation and preservation of tissues. Different foods contain different nutrients which is why it is important to include a variety of nutrient-rich foods in one’s diet. Research has shown that dietary and behavioral factors play a major role in about one-third of cancer-related deaths [10]. These factors include, but are not limited to: poor diet, high body mass index, decrease or lack of physical activity, and the use of tobacco and alcohol [6]. Studies have been conducted to see what effects dietary interventions such as low-protein diet, high fat diet, undernutrition, or caloric restriction have on epigenetic events and modifications at different stages in life, ranging from fetal growth to adulthood in human and mouse models. Strikingly, they were able to identify

epigenetic modifications that occur at each stage of development and the genes that were epigenetically regulated [11].

Upon diagnosis of chronic diseases such as cancer, cardiovascular disease, and diabetes, one of the first recommendations of health professionals is to make dietary and lifestyle changes. Improving the nutrition status and quality of life of the patient at the onset of disease can be extremely beneficial throughout therapy [10]. A number of studies have shown a correlation between diet and lifestyle factors that ultimately result in a decrease in risk of chronic diseases [12]. Key nutrients of fruits, vegetables, and whole grains may act as anti-cancer substances by suppressing biological activity required for tumor growth when consumed in amounts found in a diverse diet. These bioactive compounds have been shown to promote apoptosis as well as suppress sustained proliferative signaling and metastasis [13, 14]. Block et al. compiled epidemiological studies that focused on fruit, vegetable, and cancer prevention and found that the protective effect reported from those studies were statistically significant between individuals with cancer that consumed more fruits and vegetables than those that consumed less [15]. The belief is that epigenetic changes induced by inadequate nutrition early in life influence health and disease risk later in life [16].

MAJOR EPIGENETIC MECHANISMS

Epigenetics refer to heritable alterations that affect gene expression, resulting in changes to the function and/or regulation of the gene, without causing alterations in the DNA sequence itself [17–19]. Epigenetic mechanisms such as DNA methylation, histone modifications, and microRNA (miRNA) regulation are recognized as vital players in cancer and could possibly serve as the missing link between the genome, disease state, and environmental factors. Human cancers are defined by extensive alterations in their genomic DNA methylation, histone modification, and ncRNA expression patterns which explains why regulation is essential in all epigenetic processes. These epigenetic mechanisms may be responsible for the interindividual differences in disease risk and treatment of cancer and many other diseases.

DNA methylation involves the addition of a methyl group at the carbon-5 position of the cytosine base of CpG dinucleotides in eukaryotes. This modification is catalyzed by DNA methyltransferases (DNMTs) that exist in three major forms- DNMT1, DNMT3a, and DNMT3b. DNMT1 is primarily a maintenance methyltransferase that functions in development, whereas DNMT3a and DNMT3b facilitate *de novo* methylation [20]. DNA methylation can lead to repression or activation of transcription depending on location relative to promoters or genes [21]. DNA methylation plays a role in aging, differentiation, and responses to environmental changes [22]. In cancer, aberrant DNA methylation patterns such as hypermethylation and hypomethylation have been correlated with different stages of cancer progression and metastasis in many different tumor types [23, 24].

Histone modification plays a vital role in regulating chromatin structure and function, consequently affecting processes such as transcription and DNA repair and replication [25]. Unlike DNA methylation, histone modifications are variable and challenging to investigate [26]. Many different modifications including methylation, phosphorylation, ubiquitination,

acetylation, and sumoylation occur at the amino terminals of the core histones. During transcription, these modifications can be associated with activation or repression; however, they are not always mutually exclusive [20]. A correlation has been observed between disruption of specific histone posttranslational modifications and various cancer types [27].

miRNA, a class of short ncRNAs, are approximately 22 nucleotides (nts) in length and are involved in post-transcriptional gene silencing by interfering with the stability and translation of messenger RNAs (mRNAs) [28]. miRNAs are highly conserved between species and substantially present in all human cells [29]. miRNAs function in several biological processes such as cell growth and differentiation, apoptosis, and regulation of the cell cycle [30]. In cancer, variable expression levels of miRNA expression have been detected and data suggest that nutrients from food and dietary compounds may provide a protective mechanism against cancer via regulation of miRNAs and other ncRNAs [13]. miRNA and other long non-coding RNAs (lncRNAs) will be discussed at greater detail later in this review as they relate to nutrition and various cancers.

POTENTIAL EPIGENETIC PLAYERS: NON-CODING RNAs

Contrary to the central dogma which implies that RNA is a mere messenger between genes and the proteins they encode, ncRNAs have emerged as major transcriptional units that do not encode proteins, but have many different functions, one being regulation of gene expression [31, 32]. Only 2% of the genome is transcribed into RNAs that encode for proteins and the remainder are ncRNAs [20, 33]. ncRNAs have been found to influence all aspects of cancer biology as shown in Figure 1 [34]. There is a broad spectrum of functions that ncRNAs perform in the cell from transcriptional regulation to interacting with target proteins and mRNAs in the cytoplasm [35]. Some act at the site of transcription to regulate transcription and gene structure, while others play diverse functions away from the site of transcription in regulating other processes in the cell [35, 36]. Similar to protein-coding genes, ncRNAs have to be tightly regulated to protect the integrity of a normal cell. There are two main groups of ncRNAs- short ncRNAs that are <30 nts and long ncRNAs (lncRNAs) that are >200 nts. The short ncRNAs are further divided into three major classes: miRNA, short-interfering RNA (siRNA), and piwi-interacting RNA (piRNA).

As mentioned previously, abundantly expressed miRNA are approximately 21–23 nts in length and arise from coding and non-coding genomic regions. miRNA negatively interferes with the expression level of protein coding genes via binding to the complementary sequences in the 3' untranslated region of protein coding genes, inducing degradation or translational repression of target genes [37]. miRNAs regulate approximately 200 target mRNAs, enabling them to function at different cellular levels [38]. Aberrant expression of miRNAs is correlated with the development and progression of several cancers. miRNAs have been studied more extensively than the other ncRNAs.

On the other hand, once irrelevant, lncRNAs are emerging as novel regulatory players in complex organisms and have been shown to fulfill critical roles such as transcriptional and posttranscriptional regulation of gene expression via local gene silencing and interactions with chromatin complexes [39]. lncRNAs can be divided into five smaller groups: sense,

antisense, bidirectional, intronic, and intergenic. The majority of lncRNAs display tissue-specific patterns and the estimated number of lncRNAs in humans is 15,000 [40]. Comparable to protein-coding genes, lncRNAs have the capacity to function as tumor suppressors and oncogenes.

Some of the challenges in this field are detecting, deciphering and characterizing the ncRNAs, predicting target genes, and identifying signaling pathways [41]. Furthermore, consistent comparative data analysis in reference to dietary intake and other factors that are necessary to study the effects of dietary compounds in the modulation of ncRNAs and disease states are too variable to be conclusive. From a clinical aspect, stability, safety, specificity and effective drug delivery are always a concern and are problematic [41]. Cross validation studies are needed to corroborate individual studies that have been done in an attempt to define universal methods and analyses.

ABERRANT NON-CODING RNAs IN VARIOUS CANCERS

Tremendous efforts have gone into understanding the biology of ncRNAs in different cancers. Dysregulation of ncRNAs has been established in numerous types of cancers including colon cancer [42], hepatocellular carcinoma [43], melanoma [44] and breast cancer [45]. Aberrant expression of these ncRNAs can be associated with increased tumorigenesis on the one hand and inhibition of proliferation on the other hand. As a result of altered expressions of ncRNAs in the majority of cancer models that exist, new biomarkers and targets can be identified to aid in the progression of treatment for all cancers.

In the United States, colorectal cancer (CRC) is the third leading cause of cancer death in both men and women. According to the 2014 statistics, more men (71,830) than women (65,000) were estimated to be diagnosed with colorectal cancer as well as to succumb to the disease [46]. Treatment options include surgery, chemotherapy and radiation therapy. It has been observed that the major site of metastasis of colorectal cancer is the liver, thus leading to colorectal liver metastasis (CLM) which is difficult to treat [47]. Several studies have been launched to investigate the molecular aberrations in the occurrence of colorectal cancer with lncRNAs being a major group of interest. According to Xue et al., lncRNAs are differentially expressed between cancer and normal tissues and those differences may contribute to the important role of lncRNAs in the cancer phenotype. They concluded that lncRNAs play an important role in CRC [48]. Another group investigated the molecular mechanisms propagating cancer progression in CLM by dividing patients into three groups based on liver metastases and time after primary diagnosis of CRC. Among those three groups, differential expression of lncRNAs was observed and permitted identification of lncRNAs as biomarkers for CLM. For example, over-expression of lncRNA-CLMAT3 displayed clinical value and was associated with liver metastasis and survival among patients with CRC [49]. In addition to lncRNAs, miRNA expression is altered in malignant versus nonmalignant tumors and hypothesized to have a role in the initiation and development of CRC [50]. Many studies have focused on the expression of miRNAs in colorectal and various other cancers and have concluded that miRNAs may serve as oncogenes or tumor suppressors depending on their environment.

Hepatocellular carcinoma (HCC), a lethal liver cancer, has a very poor prognosis and is in dire need of novel targets to develop more effective treatments. The conventional treatment options of surgery and chemotherapy were limited to pre-metastatic HCC; however, a multi-kinase inhibitor, in addition to targeting other factors involved in development and progression of the disease showed promising results in advanced HCC [51]. lncRNAs such as *HOTAIR*, *MALAT1*, and *H10* are dysregulated and have been suggested to play an essential role in HCC development whereas dysregulation affects proliferation, apoptosis, and metastasis. This is also true for gastric cancer, whereby dysregulation of lncRNAs-*HOTAIR*, *HULC*, and *H19* are relatively linked to development, metastasis, and prognosis [52]. HCC is also characterized by aberrant expression of miRNAs. Respectively, upregulation and down-regulation has been associated with invasion and metastasis, tumor progression, and drug resistance. Meng et al. proposed that aberrantly expressed miRNAs may regulate the expression of certain genes that control cell growth, migration, and invasion. In this study, the expression of miRNA in normal versus tumor tissue was investigated which led to the identification of overexpressed miR-21 in human HCC that could potentially serve as a target for regulating downstream events [53].

In prostate cancer, the second most common cause of death due to cancer among men, lncRNAs such as *PCA3*, *PCGEM1*, *SchLAPI*, and *PCAT-1* have been identified for their roles as biomarkers and regulators of apoptosis and metastasis. Compared to their normal counterparts, cancer cells and tissues display elevated levels of each of those lncRNAs [54–58]. PlncRNA-1, a lncRNA also associated with apoptosis in prostate cancer, is elevated in esophageal squamous cell carcinoma (ESCC). Studies done in ESCC revealed that expression of PlncRNA-1 was considerably higher in human ESCC as compared to the adjacent normal tissue. This overexpression correlated with advanced tumor stage and metastasis [59]. Several miRNAs have been studied in prostate cancer, but mir-34 has been exceptionally attractive because it is highly evolutionarily conserved, the first miRNA found to be directly transactivated by p53, and deleted or epigenetically down-regulated in several cancer cell lines and human cancers. In mice studies using mir-34, a cooperation with p53 led to the suppression of prostate cancer, therefore elucidating the role of mir-34 as a tumor suppressor in this particular study [60].

DIETARY REGULATION OF NON-CODING RNAs AND CANCER PREVENTION

It has become increasingly evident that dietary compounds have the potential to target epigenetic mechanisms and ncRNAs. Over just the past five years, numerous studies have been conducted evaluating the role of diet in cancer epigenetics and ncRNAs *in vitro* and *in vivo*. Some of the natural agents that have been recognized as being capable of altering epigenetic mechanisms and expression profiles of ncRNA are curcumin, (-)-epigallocatechin-3-gallate (EGCG), resveratrol, and resistant starches (Table 1). This section will provide a brief overview on their epigenetic targets in different cancer forms and their roles in cancer prevention and treatment.

Curcumin, an ingredient found in the spice turmeric, has been suggested to have antiproliferative, anticancer, proapoptotic, and antioxidant properties in cancer [61]. It is currently being studied for use in many different cancers targeting tumor cells and the tumor microenvironment which is very important in the prevention and treatment of the disease. Kronski et al. showed that curcumin is capable of altering miRNA, particularly miR181b, via inducing its expression in breast cancer cells thereby leading to the down-regulation of pro-cytokines repressing their metastatic potential [62]. In pancreatic cells, curcumin treatment resulted in up-regulation of miRNA-22 and down-regulation of miRNA-199a. Further investigation in this study led to the identification of target genes of miRNA-22, *SP1 transcription factor (SP1)* and *estrogen receptor 1 (ESR1)*, whose expressions were altered upon manipulations of miRNA-22 [63]. These studies suggested mechanisms by which curcumin could exert its effects on cell proliferation and apoptosis. Although curcumin has advanced to phase 1 clinical trials as a result of its diverse effect and proven safety at relatively high doses, the bioavailability of this compound is problematic; however, alternative mechanisms to overcome this problem are being investigated [64, 65].

EGCG, derived from green tea polyphenols (GTPs), has been shown to have anticancer effects via inhibition of the human telomerase reverse transcriptase (hTERT), DNMTs, and histone acetyltransferases (HATs) [66, 67]. Tsang and his colleagues observed that EGCG treatment in human hepatocellular carcinoma HepG2 cells modified the expression of a total of 61 miRNAs. One in particular, miR-16, was up-regulated by EGCG and resulted in down-regulation of the anti-apoptotic Bcl-2 and induction of apoptosis. They also found that upon suppression of miR-16, Bcl-2 expression increased [68]. In human and mouse lung cancer cells, EGCG up-regulation of miR-210 led to a reduction in cell proliferation, anchorage-independent growth, and sensitivity to EGCG thereby contributing to the anticancer activity exhibited by this compound. The upregulation of miR-210 after EGCG treatment correlated with the stabilized HIF-1 α in the lung cancer cells [69].

Resveratrol, another polyphenol, has been studied in multiple cancers and has been shown to offer anti-cancer effects inhibiting tumor initiation and progression pathways [70]. Liu et al. investigated the mechanism of resveratrol in various pancreatic cell lines and its effect on mir-21 expression in those cell lines. Resveratrol significantly inhibited cellular proliferation and decreased the expression of mir-21. They concluded that down-regulation of mir-21 by resveratrol inhibited Bcl-2 expression in the pancreatic cancer cell lines promoting apoptosis [71]. In colorectal cancer, the over-expression of lncRNA MALAT-1 correlates to metastasis. Ji et al. screened Chinese anticancer drugs for their effect in colorectal cancer cells and on the inhibition of MALAT-1. Of all of the candidates screened, resveratrol was one of the two compounds that inhibited MALAT-1 and was the best compared to osthole, the second compound. Further investigation, revealed that MALAT-1 over-expression promoted proliferation and invasion in the cells; however, treatment using resveratrol reversed the proliferation, invasion, and metastasis cascade initiated by over-expression of MALAT-1 via blocking key events in the Wnt/ β -catenin signaling pathway [72].

Resistant starches are indigestible nutrient carbohydrates that have been shown to have an impact in human health [73]. Resistant starches can be found in foods such as green bananas, cashews, sweet potatoes, steamed and cooled potatoes, roasted and cooled potatoes,

and cooked and cooled potatoes. Cooling after the initial preparation has been shown to yield significant increase in resistant starch [74, 75]. In a paper published by K.J. Humphreys et al. the effect of a high red meat (HRM) diet and butyrylated resistant starch on miRNA expression in healthy volunteers was examined. Similar to what is observed with lncRNA MALAT-1 in colorectal cancer, there is also increased expression of miRNAs in colorectal cancer. The miRNAs that were affected by the diets were miR17-92 cluster, increased with the HRM diet, but restored to baseline level upon supplementation with butyrylated resistant starch and miR21 which was also increased with the HRM diet; however, no restoration upon butyrylated resistant starch. The trials conducted with the HRM diet and butyrylated resistant starch revealed a possible protective effect of butyrylated resistant starch via altering the miRNA levels that were increased in response to the HRM diet [76].

CONCLUSIONS

The area of nutrition and gene expression has grown immensely and is forging the way for novel targets and improved treatments. What we have learned over the past decade is that genetic and epigenetic alterations contribute to the growth of cancer. We know that nutrients and bioactive food components can control epigenetic phenomena and that it can be extremely difficult and time consuming to identify and investigate the exact effects of nutrients in every epigenetic event, as well as their associations with natural and disease processes in the body. Nevertheless, it is still imperative to test more nutrients or natural compounds and aim to discover more ncRNAs to find enhanced alternatives for our health. One class of ncRNAs, particularly, miRNAs, have been extensively studied with respect to expression and regulation by dietary compounds, whereas little to no data have been presented for the regulation of lncRNAs by dietary compounds. Further elucidation of ncRNAs and their regulation by dietary compounds would be beneficial in providing a better way to protect our health with nutritional variation that is more physiological than pharmacological. Understanding the role of diet in altering epigenetic patterns could potentially lead to the development of new strategies for disease prevention.

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LIST OF ABBREVIATIONS

DNMTs	DNA methyltransferases
mRNA	Messenger RNA
miRNA	MicroRNA
ncRNA	Non-coding RNA
lncRNA	Long non-coding RNA

siRNA	Short-interfering RNA
piRNA	Piwi-interacting RNA
CRC	Colorectal cancer
CLM	Colorectal liver metastasis
HCC	Hepatocellular carcinoma
nts	Nucleotides
EGCG	(-)-epigallocatechin-3-gallate
SP1	SP1 transcription factor
ESR1	Estrogen receptor 1
GTP	Green tea polyphenols
hTERT	human telomerase reverse transcriptase
HAT	Histone acetyltransferases
ESCC	Esophageal squamous cell carcinoma
PCA	Prostate cancer antigen 3
PCGEM1	Prostate-specific transcript 1 (non-protein coding)
MALAT-1	Metastasis Associated Lung Adenocarcinoma Transcript 1 (non-protein coding)
HOTAIR	HOX transcript antisense RNA
HRM	High red meat

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Figure 1. Non-coding RNAs. Summary of the functions of non-coding RNAs and the hallmarks of cancer that are achieved by those actions. The red arrows denote phytochemicals that can alter the expression of non-coding RNAs leading to the regulation of cellular activity (outer circles) that has been shown to be induced upon dysregulation of non-coding RNAs in various cancers.

Table 1

Dietary regulation of non-coding RNAs in various cancer types.

Dietary chemicals	Altered Expression of Non-coding RNAs	Cancer Types	Modes of action	References
Curcumin	miR181b	Breast	Down-regulation of cytokines	[62, 63]
	miRNA-22	Pancreatic	Alters expression of target genes <i>SP1 transcription factor</i> and <i>estrogen receptor 1</i>	
EGCG	miR-16	Human hepatocellular carcinoma	Down-regulation of anti-apoptotic Bcl-2	[68, 69]
	miR-210	Human and mouse lung cancer	Reduction in cell proliferation, anchorage-independent growth	
Resveratrol	miR-21	Pancreatic	Inhibits Bcl-2	[71, 72]
	MALAT-1	Colorectal	Promotes proliferation and invasion in the cells	
Butyrylated resistant starch	miR17-92 cluster miR-21	Colorectal	Promotes proliferation and angiogenesis; induces tumorigenesis, invasion, and metastasis	[76]