

MicroRNA and Cancer Chemoprevention

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Abstract

MicroRNAs (miRNA) are a group of naturally occurring, small, noncoding, and single-strand RNA molecules that regulate gene expression at the posttranscriptional and translational levels. By controlling the expression of oncogenic and tumor suppressor proteins, miRNAs are believed to play an important role in pathologic processes associated with malignant progression including tumor cell proliferation, apoptosis, differentiation, angiogenesis, invasion, and metastasis. However, relatively few studies have investigated the influence of chemopreventive agents on miRNA expression and their regulation of target genes. Given the significance of miRNAs in modulating gene expression, such research can provide insight into the pleiotropic biologic effects that chemopreventive agents often display and a deeper understanding of their mechanism of action to inhibit carcinogenesis. In addition, miRNAs can provide useful biomarkers for assessing antineoplastic activity of these agents in preclinical and clinical observations. In this review, we summarize recent publications that highlight a potentially important role of miRNAs in cancer chemoprevention research. *Cancer Prev Res*; 6(5); 401–9. ©2013 AACR.

Introduction

MicroRNAs (miRNA) are a class of noncoding small (averaging 20 nucleotides) RNA molecules that negatively regulate gene expression by repressing translation or affecting mRNA stability (1, 2). Because of their central role in regulating gene expression, miRNAs have been recognized as "master" regulators of a multitude of cellular functions. The latest version of miRbase (ver. 19) reports 21,264 entries for 193 species in which about 2,000 human miRNA sequences have been defined (<http://www.mirbase.org>). The small amount of miRNAs accounts for 1% to 3% of human genome but they are known to regulate more than 30% of human genes (2). A single miRNA can regulate hundreds of putative target genes, whereas a single gene can be simultaneously regulated by multiple miRNAs (3). The biogenesis of miRNAs is similar to other RNA molecules starting from DNA transcription. Immature primary miRNAs (pri-miRNAs) are generated from the transcription of miRNA genes mediated by RNA polymerase (4). Before becoming mature miRNAs, pri-miRNAs need to be cleaved by the nuclear microprocessor complex consisting of the RNase III (Drosha) and the co-factor DGCR8 (DiGeorge critical region 8) to form precursor miRNAs (pre-miRNAs) that are approximately 70 nt in length (5). By the nuclear export factor, Exportin 5, pre-miRNAs can be transported to

the cytoplasm where they are bound by the RNase III-type endonuclease, Dicer, which can cleave the hairpins of pre-miRNAs to form the double-stranded RNA duplexes (6). Ago2 protein is involved in the dissociation of these RNA duplexes and formation of single-stranded mature miRNAs (7). Thereafter, mature miRNAs bind with the RNA-induced silencing complex (RISC) to functionally regulate the expression of the target genes. The process of miRNA biogenesis and their central function in regulating gene expression are illustrated in Fig. 1.

Various miRNAs have been shown to control cell growth, differentiation, and apoptosis (8–10). Consistent with these reports, impaired miRNA expression has been implicated in tumorigenesis (8). Such observations suggest an important role of miRNAs in regulating cellular processes associated with malignant progression, although we are at an early stage of understanding how this important class of gene regulators is involved in cancer-related processes. The first indication that miRNAs might function as tumor suppressors was suggested in a study by Calin and colleagues, who found that miR-15a and miR-16-1 were commonly deleted in more than 65% of patients with B-cell chronic lymphocytic leukemia (11). Another study showed that miR-15a and miR-16-1 negatively regulated Bcl2, an anti-apoptotic protein often overexpressed in many tumor types (12). More than 50% of genes that are regulated by miRNAs are located in cancer-associated genomic regions or in sites of genomic instability (13). These observations suggest the importance of miRNAs in the pathogenesis of human cancers (14). MiRNAs can act as either oncogenes or tumor suppressors, depending on the function of their target genes. Many oncogenic miRNAs have been studied and found to contribute to certain hallmarks of cancer, such as sustaining proliferative signaling, resisting growth suppression and apoptosis, enabling replicative immortality,

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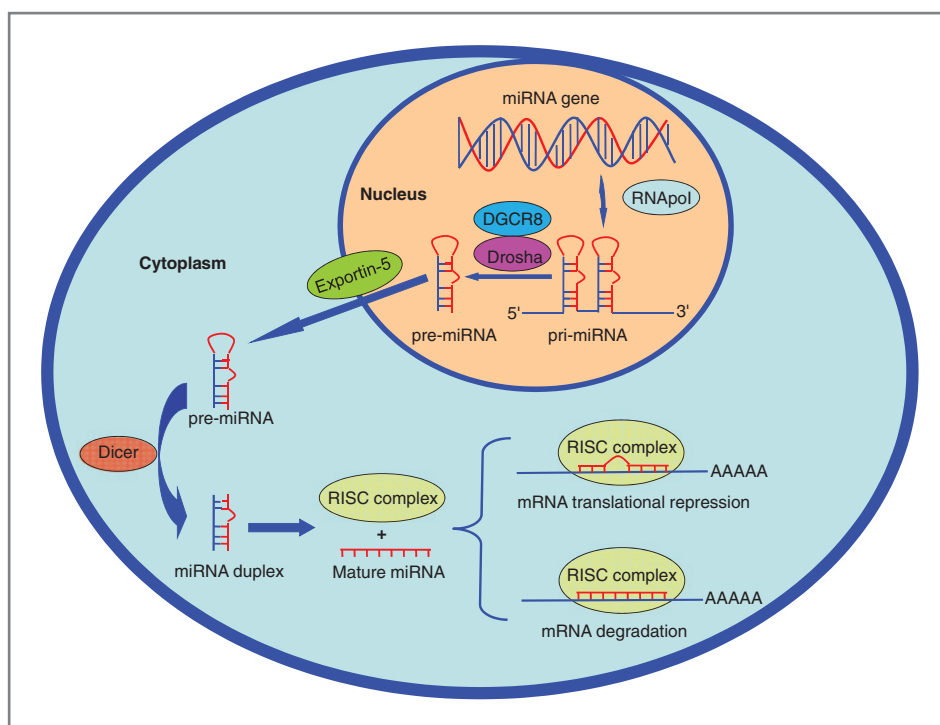


Figure 1. Biogenesis of miRNAs and mechanism that miRNAs repress gene expression.

prompting angiogenesis, invasion and metastasis, evading immune detection, reprogramming energy metabolism, improving tumor promoting inflammation, and maintaining genome instability and mutations (15–21). Therefore, the dysregulation of miRNAs could be of importance for the initiation, development, and progression of cancer.

Cancer chemoprevention refers to the use of chemical agents that occur naturally in food or administered as pharmaceuticals to inhibit or reverse the process of carcinogenesis (22, 23). Although alteration of different miRNAs is often found in various human cancer types following treatment with certain chemopreventive agents, their role in cancer chemoprevention has not yet been well understood. As master regulators of gene expression, the involvement of miRNAs in mediating the response could explain the often complex pleiotropic biologic activities of chemopreventive agents through their suppressive effects on multiple target genes. Therefore, it is significant to study miRNA in chemoprevention to gain a better understanding of the mechanisms by which natural products and pharmaceuticals prevent human cancers. To complement previous review articles on this topic (20, 21, 24–26), we will focus on summarizing the regulation of miRNAs by diverse classes of cancer chemopreventive agents.

MiRNA and Natural Products

Vitamin A

All-*trans* retinoic acid (ATRA) is a metabolite of vitamin A that is responsible for many of the effects of vitamin A associated with cell proliferation and differentiation (27). Using acute promyelocytic leukemia cell lines treated with ATRA, miR-15a, miR-15b, miR-16-1, let-7a, let-7c, let-7d,

miR-223, miR-342, and miR-107 were shown to be induced, whereas miR-181b was suppressed (28). In support of this finding, the similar expression patterns of these miRNAs were found in patients treated with ATRA and chemotherapy (29). Upregulation of let-7a, miR-15a, and miR-16-1 was shown to mediate the antiproliferative activity of ATRA, which partially attributed to suppression of 2 oncogenes, Ras and Bcl-2 (28). Moreover, the mechanism by which ATRA affect miRNA expression was found to involve the modulation of NF- κ B at the transcriptional level (28, 29). In another study, ATRA was reported to induce the expression of miR-186, miR-215, and miR-223 but reduce the expression of miR-17-5p, miR-25, miR-193, miR-195, and let-7a in human NB4 promyelocytic leukemia cells (30). Zhong and colleagues also found that miR-146a downregulation by ATRA treatment played an important role in influencing proliferation of NB4 cells, which was mediated by the TGF- β pathway involving SMAD4 targeted by miR-146a (31). A recent study showed that miR-29a and miR-142-3p could promote ATRA-induced granulocytic differentiation in human leukemia HL-60, THP-1, and NB4 cells (32). In breast cancer, ATRA was reported to induce the expression of pro-oncogenic miR-21 in MCF-7 cells. Upregulation of miR-21 reduced the expression of maspin, which is involved in ATRA-induced tumor growth inhibition and contributed to the suppression of cell motility (33).

Vitamin B

Folate is the form of water-soluble vitamin B₉ and is thought to have cancer preventive benefits. For example, high levels of dietary folates have been reported to reduce

the risk of gastrointestinal tumors (34). According to Marsit and colleagues, miR-222 was upregulated in lymphoblastoid cells cultured in folate-deficient media. When folate was added to the media, the expression of miR-222 reversed to the level in folate-deficient media (35). In addition, miR-122 was found to be suppressed in hepatocellular carcinomas (HCC) that developed in male Fisher rats fed diet deficient in folic acid, methionine, and choline. However, this miRNA was expressed in the rats without tumor burden (36). These results imply that miRNAs have the potential to become valuable biomarkers of carcinogenesis, and their expression levels are associated with sufficient supply of certain nutritional agents such as vitamin B.

Vitamin D

Vitamin D is a well-studied chemopreventive agent that has been tested *in vitro* for the ability to regulate miRNA expression in a variety of human cell lines. In human myeloid leukemia cells, 1,25-dihydroxyvitamin D(3) was shown to upregulate miR-32 (37), whereas miR-181 was repressed, both in a time- and dose-dependent manner (38). As p27(Kip1) is a target gene of miR-181, the downregulation of miR-181 and subsequent elevation of p27 (Kip1) may mediate the arrest of the cell cycle at G₁ phase by 1,25-dihydroxyvitamin D(3) (38). Peng and colleagues found that the metabolite of vitamin D, 25-hydroxyvitamin D(3) protected breast epithelial MCF12F cells from variable cellular stress conditions such as serum starvation, hypoxia, oxidative stress, and apoptosis induction. Microarray analysis found that many miRNAs including miR-182 could be altered by serum starvation, whereas 25-hydroxyvitamin D(3) counteracted this action and stabilized the expression of these miRNAs (39). A recent publication reported that miR-98 can be upregulated by 1,25-dihydroxyvitamin D(3) in prostate cancer cells and is involved in inhibition of tumor cell growth by inducing G₂-M arrest (40). The stability of vitamin D receptor (VDR) is important for the transduction of vitamin D signaling in prevention of human cancer. MiR-125b and miR-27b were found to directly target VDR in different tumor cell lines and may mediate the anticancer activities of vitamin D (41–43). In colon cancer cells, miR-22 could be induced by 1,25-dihydroxyvitamin D(3) in a time-, dose-, and VDR-dependent manner, whereas in patient tissue specimens, miR-22 levels chiefly correlated with the expression of VDR (44). These observations highlight an important role of miRNAs in mediating the chemopreventive activities of vitamin D.

Vitamin E

Epidemiologic studies have reported the preventive activity of vitamin E in various cancer types (45), although the influence of vitamin E on miRNA expression has not been well-studied. An *in vivo* study by Gaedicke and colleagues reported that rats fed by diets deficient in vitamin E could decrease the expression of miR-122a and miR125b (46). As miR-122a is associated with lipid metabolism and miR-125b is relevant to inflammation and tumorigenesis in liver, these results suggest that dietary vitamin E may affect

miRNAs that regulate activities associated with hepatocyte function.

Fatty acids

N-3-polyunsaturated fatty acids (n-3 PUFAs) are found in fish oil and green leafy vegetables known to have cancer chemopreventive benefits (47). Using the rat azoxymethane (AOM) model of colon tumorigenesis, Davidson and colleagues studied ectopically expressed miRNAs in the progression of colorectal cancer (48). Aside from reporting the dysregulation of a number of miRNAs in adenocarcinomas from AOM-injected animals compared with normal mucosa from saline-injected controls, they found that fish oil added to the diet could significantly counteract the effect of AOM on miRNA expression (48). For example, let-7d, miR-15b, miR-107, miR-191, and miR-324-5p were found to be downregulated in tumor tissues compared with normal mucosa controls, but their expression was rescued by the treatment with fish oil (48). These results indicate that miRNAs can be regulated by n-3 PUFAS to protect against colon carcinogenesis.

Curcumin

Curcumin is a bioactive compound derived from the turmeric that is known to have suppressive effects on inflammation, oxidative damage, and carcinogenesis (49). Curcumin was found to inhibit the expression of miR-21 through the transcriptional regulation of activator protein-1 (AP-1) in colon Rko and HCT116 tumor cells. As miR-21 is a known oncogene, its downregulation is associated with the suppression of cell proliferation, tumor growth, invasion, and metastasis, partially through the upregulation of the tumor suppressor, programmed cell death protein 4 (PDCD4; ref. 50). Curcumin was also found to induce miR-22 and repress miR-199a in human pancreatic PxBc-3 tumor cells (51). The repressive effects of miR-22 on estrogen receptor 1 (ESR1) and transcription factor SP1 might mediate the antiproliferative activity of curcumin, which is known to have multiple biologic activities (51).

Resveratrol

Resveratrol is a natural antioxidant with chemopreventive properties that can be isolated from various fruits such as red grapes (52). In human acute monocytic leukemia THP-1 cells, resveratrol could upregulate the expression of miR-663, which can decrease the expression levels of JunB/D and the activity of AP-1 (53). In addition, resveratrol can impair the induction of oncogenic miR-155 by lipopolysaccharides (LPS) in an miR-663-dependent manner (53). Using microarray technology, Dhar and colleagues found that resveratrol treatment could induce 28 miRNAs with tumor suppressor characteristics and inhibit up to 23 oncogenic miRNAs in prostate cancer, which included a few well-known miRNA clusters such as miR-17-92 and miR-106 (54).

Ellagitannin

Ellagitannin, a natural product found in fruit and nut, such as strawberry and walnut, is reported to have

chemopreventive activity (55, 56). Wen and colleagues reported that ellagitannin (BJA3121) can regulate the expression of 25 miRNAs in human hepatocellular carcinoma HepG2 cells, including 17 upregulated and 8 down-regulated miRNAs (57). Of these miRNAs, upregulation of let-7e, miR-370, miR-373*, and miR-526b and downregulation of let-7a, let-7c, and let-7d by BJA3121 were confirmed to be affected in a time- and dose-dependent manner (57). Ai and colleagues also found that ellagitannin (BJA32515) could inhibit tumor cell proliferation and induce apoptosis of HepG2 cells, which might be attributed to the upregulation of let-7a/miR-29a and the downregulation of miR-197/373 by ellagitannin (58).

Genistein

Genistein is an isoflavone that has a high content in soybean and has been extensively studied for its chemopreventive activity (59). Sun and colleagues reported that miR-27 together with its target gene, zinc finger BTB domain containing 10 (ZBTB10), mediates the anticancer activity of genistein in human uveal melanoma cells *in vitro* and *in vivo* (60). Moreover, genistein treatment could repress the expression of miR-221/222, which upregulate the expression of the tumor suppressor ARHI in human prostate PC3 tumor cells (61).

Catechins

Epigallocatechin-3-gallate (EGCG) and other catechins are polyphenols that can be extracted from green tea and are well documented for their chemopreventive properties in various types of human cancer. Chakrabarti and colleagues reported in human malignant neuroblastoma cells that EGCG treatment could induce apoptosis, whereas the combination of *N*-(4-hydroxyphenyl) retinamide (4-HPR) and EGCG could inhibit tumor cell growth, in which downregulation of oncogenic miRNAs (miR-92, miR-93, and miR-106b) and upregulation of (miR-7-1, miR-34a, and miR-99a) were reported (62, 63). MiR-210 is a hypoxia-regulated miRNA under the control of hypoxia-inducible factor 1 (HIF-1) at the transcriptional level (64). HIF-1 and miR-210 are commonly elevated in tumor cells grown in a hypoxic microenvironment. Wang and colleagues reported that EGCG was able to suppress human and mouse lung cancer cell growth through the upregulation of miR-210 by stabilizing the transcriptional activity of HIF-1 (65). In advanced prostate cancer, EGCG could antagonize androgen action to inhibit tumor cell growth. *In vivo* results showed that EGCG could reduce the expression of androgen-regulated oncogenic miR-21 and induce the tumor-suppressive miR-330 (66). Moreover, Tsang and colleagues showed that EGCG treatment could induce apoptosis in human hepatocellular carcinoma HepG2 cells, which were, in part, attributed to the upregulation of miR-16 and its subsequent repression on oncogene Bcl-2 (67).

Indoles

Indole-3-carbinol (I3C) is derived from cruciferous vegetables in which its *in vivo* metabolite is 3, 3'-diindolyl-

methane (DIM). Melkamu and colleagues reported that I3C counteracted the toxicity of the carcinogen, vinyl carbamate (VC) *in vivo*. VC caused lung tumor in female A/J mice in which miR-21, miR-31, miR-130a, miR-146b, and miR-377 were upregulated, whereas miR-1 and miR-143 were downregulated. However, the oncogenic induction of miR-21, miR-31, miR-130a, miR-146b, and miR-377 in mice was attenuated by supplying I3C in the diet (68). DIM has also been reported to inhibit the epithelial-to-mesenchymal transition (EMT) in gemcitabine-resistant pancreatic cancer cells, in which let-7b, let-7c, let-7d, let-7e, miR-200b, and miR-200c were significantly upregulated by drug treatment. The functional studies revealed that DIM treatment could suppress mesenchymal markers, ZEB1, slug, and vimentin, which appeared to be a similar phenotype caused by re-expression of miR-200b (69). Jin and colleagues found that DIM could reduce the cell growth of breast cancer cells *in vitro* and inhibit development of the mammary tumor *in vivo*, whereas G₂-M cell-cycle arrest caused by DIM repression of cyclin-dependent kinases 2 and 4 (CDK2/4) and cell division cycle 25 homolog A (Cdc25A) were responsible for the anticancer activity of DIM (70). Intriguingly, miR-21 was found to be induced by DIM and subsequently repressed the expression of Cdc25A, although this miRNA is well-known for its oncogenic activity (71-73).

MiRNA and Pharmaceuticals

Estrogen receptor antagonists

Tamoxifen is an antagonist of the estrogen receptor in breast tissue and used to treat hormone receptor-positive breast cancer in pre- and postmenopausal women (74). Tamoxifen has been approved by the U.S. Food and Drug Administration for the prevention of breast cancer in high-risk women. Miller and colleagues reported the ectopic upregulation miR-221/222 in HER2/neu-positive primary human breast cancer tissues that are known to be resistant to endocrine therapy. *In vitro* studies showed that overexpression of miR-221/222 can render human breast MCF-7 tumor cells resistant to tamoxifen (75). These results were supported by another study showing that miR-221/222 is elevated in estrogen receptor α (ER α)-negative breast cancer cells when compared with ER α -positive cells, suggesting that miR-221/222 may be responsible for resistance to the estrogen therapy in a subset of breast cancers by regulating ER α expression (76). Downregulation of miR-342 was found to be associated with the resistance to tamoxifen in breast tumor cells and clinical tissue specimens. Restoring of miR-342 could significantly improve the sensitivity of breast cancer cells to tamoxifen by inducing apoptosis and inhibiting tumor cell growth. These results provide insight into the treatment of breast cancers that are resistant to tamoxifen (77).

Fulvestrant is another estrogen receptor antagonist and a selective estrogen receptor downregulator (SERD) that can prevent the normal cellular responses to estrogen. Fulvestrant is used for treatment of hormone receptor-positive patients with metastatic breast cancer with disease progression following antiestrogen therapy (78). Rao and

colleagues found that miR-221/222 are overexpressed in the breast cancer cells resistant to fulvestrant and were responsible for tumor cell growth and cell-cycle progression. Ectopic upregulation of miR-221/222 in ER α -positive cell lines protected against the effects of estradiol depletion or fulvestrant-induced cell death. Mechanistic studies revealed that the signaling pathways mediated by β -catenin and TGF- β accounted for oncogenic roles of miR-221/222 in fulvestrant-resistant breast cells (79).

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAID) are a chemically diverse family of drugs commonly used to treat a variety of inflammatory conditions and pain associated with arthritis. The long-term use of NSAIDs has been shown to significantly reduce the incidence and risk of death from colorectal, breast, and other forms of cancer (80). COX-2 is inducible at sites of inflammation and cancer. The antineoplastic activity of NSAIDs is generally believed to be attributed to inhibition of COX-2, which leads to reduced levels of prostaglandins that inhibit apoptosis and stimulate angiogenesis and invasion, whereas Bcl-2, Akt, and IL-6 were reported to be involved in these anticancer actions associated with COX-2 inhibition (81). Celecoxib is a NSAID that can selective inhibit COX-2 with potential for the prevention of colorectal cancer based on the results from large-scale randomized clinical trials (82). However, COX inhibition is associated with potentially fatal gastrointestinal, renal, and cardiovascular toxicity. As a result, long-term administration of NSAIDs for cancer prevention is not recommended (83). Recently, Saito and colleagues reported the tumor-suppressive property of miR-29c in gastric cancer, and its ectopic downregulation was associated with the progression of this disease. Celecoxib could induce the expression of miR-29c and repress the expression of the oncogene Mcl-1 that was targeted by miR-29c (84). These results suggest that miR-29c and its target genes may mediate the anticancer activity of celecoxib in gastric cancer cells.

We recently reported that the NSAID, sulindac sulfide (SS), can inhibit tumor cell invasion by a distinct mecha-

nism from its COX-inhibitory activity (85). Although the anticancer activities of sulindac have been widely reported to involve the inhibition of tumor cell proliferation and induction of apoptosis (86–88), few studies have investigated their effect on tumor cell invasion and metastasis. This inhibitory activity by SS was found to be associated with significant changes in miRNA expression, which we suspect is responsible for the complex pleiotropic anticancer activity of sulindac. Using microarray analysis, we found that SS treatment could alter the expression of 132 miRNAs (17 up and 115 down) in human HCT116 colon tumor cells, in which several have been previously reported to promote tumor metastasis and invasion, such as miR-10b, miR-17, miR-21, and miR-9 (89–95). These observations suggest that miRNAs are involved in the anticancer activities of certain chemopreventive NSAIDs. Moreover, our analysis of the miRNA promoter sequences that were suppressed by SS revealed that 81 of 115 sequences contained NF- κ B-binding sites. Functional studies showed that SS can inhibit the translocation of NF- κ B to the nucleus by decreasing the phosphorylation of IKK β and I κ B, which, in turn, led to suppression of the miRNA expression as shown in Fig. 2. Therefore, we showed that miRNAs are functionally involved in the anti-invasive activities of SS (85).

Summary and Perspective

A number of publications have reported the potential of miRNAs as a class of novel biomarkers in response to various chemopreventive agents (20, 21, 24–26). Tables 1 and 2 summarize the chemopreventive agents consisting of either natural products or pharmaceuticals that can influence the expression of numerous miRNAs in different types of human cancer. Of significance, many of these miRNAs, such as let-7, miR-21, and miR-221/222, are found to be targeted by multiple chemopreventive agents (28, 29, 35, 50, 57, 61, 66–68, 70, 75, 76, 79, 85). Given that these miRNAs play an important role in the cellular processes involved in development and progression of cancer, it is likely that they can provide useful insight into studying the mechanisms responsible for the antineoplastic activity of various chemoprevention agents, especially for those that

Figure 2. SS regulates the expression of miRNAs through the NF- κ B signaling at the transcriptional level.

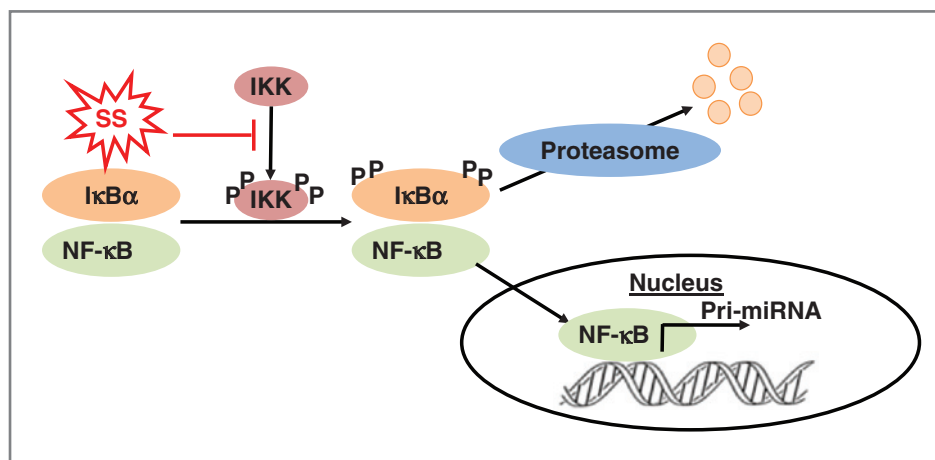


Table 1. MiRNAs and natural products in cancer chemoprevention

Natural products	Models	Upregulation	Downregulation	Ref
Vitamin A	Human leukemia cells	miR-15a, miR-15b, miR-16-1, let-7a-3, let-7c, let-7d, miR-223, miR-342, miR-107	miR-181b	(28, 29)
	Human leukemia cells	miR-186, miR-215, miR-223	miR-17-5p, miR-25, miR-193, miR-195, let-7a	(30)
	Human leukemia cells		miR-146a	(31)
Vitamin B (folate)	Human breast cancer cells	miR-21		(33)
	Human lymphoblast cells	miR-222		(35)
Vitamin D	Fisher rats		miR-122	(36)
	Human leukemia cells	miR-32		(37)
	Human leukemia cells		miR-181	(38)
	Human breast cancer cells	miR-182		(39)
	Human prostate cancer cells	miR-98		(40)
Vitamin E	Human colon cancer cells and patient samples	miR-22		(44)
	Male Fisher 344 rats		miR-122a, miR-125b	(46)
Fatty acids	Rat AOM model	let-7d, miR-15b, miR-107, miR-191, miR-324-5p		(48)
Curcumin	Human colon cancer cells		miR-21	(50)
	Human pancreatic cancer cells	miR-22	miR-199a	(51)
Resveratrol	Human acute monocytic leukemia cells	miR-663	miR-155	(53)
	Human prostate cancer cells		miR-17-92, miR-106a/b	(54)
Ellagitannins	Human hepatocellular carcinoma cells	let-7e, miR-370, miR-373*, miR-526b	let-7a, let-7c, and let-7d	(57)
	Human hepatocellular carcinoma cells	let-7a, miR-29a	miR-197, miR-373	(58)
Genistein	Human uveal melanoma cells		miR-27	(60)
	human prostate cancer cells		miR-221, miR-222	(61)
Catechins	Human malignant neuroblastoma cells	miR-7-1, miR-34a, miR-99a	miR-92, miR-93, miR-106b	(62, 63)
	Human and mouse lung cancer cells	miR-210		(65)
	Human prostate cancer cells	miR-330	miR-21	(66)
	Human hepatocellular carcinoma cells	let-7a, miR-16, miR-221	miR-18a, miR-34b, miR-193b, miR-222, miR-342	(67)
Indoles (I3C and DIM)	Female A/J mice	miR-21, miR-31, miR-130a, miR-146b, miR-377	miR-1, miR-143	(68)
	Human pancreatic cancer cells	let-7b, let-7c, let-7d, let-7e, miR-200b, miR-200c		(69)
	Human breast cancer cell line	miR-21		(70)

have complex pleiotropic effects on cancer cells. In addition to the discovery and validation of novel miRNAs, in the future, it will be significant to study the mechanism by which chemopreventive agents regulate miRNAs and how miRNAs are involved in anticancer activities of these agents. For examples, the transcription factors NF- κ B and AP-1 were reported to link differentiated expression of miRNAs with regulatory activity of certain chemopreventive agents such

as vitamin A, sulindac, curcumin, and resveratrol (28, 29, 50, 57, 85). These efforts may shed light on the complex biologic mechanisms by which many chemopreventive agents appear to act on cancer cells.

In summary, miRNAs are important regulators of oncogenes and tumor suppressor genes that are responsible for pathologic processes associated with malignant progression. Better understanding of the role of miRNAs in the

Table 2. MiRNAs and pharmaceuticals in cancer chemoprevention

Pharmaceuticals	Models	Upregulation	Downregulation	Ref
Estrogen receptor antagonist				
Tamoxifen	Human breast cancer cells		miR-221, miR-222	(75, 76)
	Human breast cancer cells	miR-342		(77)
Fulvestrant	Human breast cancer cells		miR-221, miR-222	(79)
NSAIDs				
Celecoxib	Human gastric cancer cells	miR-29c		(84)
Sulindac	Human colon and breast cancer cells		miR-10b, miR-17, miR-21, miR-9	(85)

anticancer activities of chemopreventive agents can provide insight into the discovery of novel biomarkers and establishment of new strategies to study the underlying biologic processes involved in carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G.A. Piazza, Y. Xi

Development of methodology: Y. Xi

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Xi

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Xi

Writing, review, and/or revision of the manuscript: B. Yi, G.A. Piazza, X. Su, Y. Xi

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Xi
Study supervision: Y. Xi

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