The Emerging Role of microRNAs and Nutrition in Modulating Health and Disease

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Abstract

Understanding the molecular mechanisms that inform how diet and dietary supplements influence health and disease is an active research area. One such mechanism concerns the role of diet in modulating the activity and function of microRNAs (miRNAs). miRNAs are small noncoding RNA molecules that are involved in posttranscriptional gene silencing and have been shown to control gene expression in diverse biological processes including development, differentiation, cell proliferation, metabolism, and inflammation as well as in human diseases. Recent evidence described in this review highlights how dietary factors may influence cancer, cardiovascular disease, type 2 diabetes mellitus, obesity, and nonalcoholic fatty liver disease through modulation of miRNA expression. Additionally, circulating miRNAs are emerging as putative biomarkers of disease, susceptibility, and perhaps dietary exposure. Research needs to move beyond associations in cells and animals to understanding the direct effects of diet and dietary supplements on miRNA expression and function in human health and disease.

Contents

INTRODUCTION

There is much evidence, including preclinical, epidemiological, and clinical, that diet is one of the most important modifiable determinants of health and disease. The biological and molecular underpinnings that describe how diet influences health and disease are current focuses of active research. One underpinning involves understanding gene regulation, including the role of diet in modulating noncoding regulatory RNA such as microRNAs (miRNAs or miRs). miRNAs are small, single-stranded noncoding RNA molecules [containing from 18–25 nucleotides (nts)] that participate in posttranscriptional gene regulation by binding (generally with imprecise complementarity) to the 3′-UTR of a target messenger RNA (mRNA), resulting in degradation or inhibition of translation (34). Each miRNA is thought to have several targets, and more than one miRNA can converge on a single mRNA, suggesting the enormous regulatory role for these interesting molecules (116). Approximately 2,000 human miRNA sequences have now been identified (81), and it has been projected that they likely regulate two-thirds of the human genome (107).

The first miRNAs to be discovered, lin-4 and lethal-7 (let-7), were found to be essential for developmental timing in *Caenorhabditis elegans* (133). Subsequently, a mammalian let-7 family has been identified and characterized with twelve members expressed from eight distinct loci (let-7a-1, -2, -3; let-7b; let-7c; let-7d; let-7e; let-7f-1, -2; let-7g; let-7i; miR-98) (122). Although distributed throughout the genome, many let-7 miRNA family members are coordinately regulated during development, and their regulation has been shown to involve RNA-binding proteins, including Lin28, which inhibits let-7 biogenesis.

In addition to developmental stage–specific expression, miRNA expression appears to change with adult age, is tissue specific, and may define the physiological context of the cell, including disease (132). As an example, distinct miRNA expression patterns were exclusive to certain cancers and reflected the developmental lineage and differentiation status of tumors (70). The proposed function of miRNAs in health and disease has been strengthened by the observation that many miRNAs perform key roles in critical biological processes, such as proliferation, cell cycle progression, and apoptosis, as well as differentiation and maintenance of stem cells (76).

With the exception of lin-4 and let-7, miRNAs are named numerically in sequential order of discovery (9). A lower-case "mir-" usually refers to the precursor form, while a capitalized "miR-" denotes the mature miRNA. The numerical names are preceded by 3 letters signifying the species of origin, such as "hsa-" for *Homo sapiens* and "mmu-" for *Mus musculus*. Relationships among

miRNAs can be inferred by the naming scheme. For example, paralogous miRNAs with nearly identical structure and sequencing are noted with a lowercase letter (e.g., miR-34b is closely related to miR-34c) (43).

miRNAs are synthesized through a sequential process that comprises a number of enzymes and proteins. miRNAs are initially transcribed by RNA polymerase II as long primary transcripts (pri-miRNA) from either intergenic regions or introns (120). The pri-miRNA is recognized and cleaved by the RNAase III Drosha and the RNA binding protein DiGeorge syndrome critical region 8 (DGCR8) complex to produce the precursor miRNA (pre-miR). Once formed, the pre-miR is transferred to the cytoplasm by the nuclear export factor exportin 5 for further processing by the RNAase III enzyme Dicer, resulting in an ~22-nt-long miRNA:miRNA* duplex. Thereafter, one miRNA strand (guide or mature strand) of the duplex is loaded onto a multiprotein complex to form the RNA-induced silencing complex (RISC) to regulate target mRNA; the other strand (passenger strand or miRNA*) is released and rapidly degraded (115). Usually the miRNA strand with the thermodynamically less stable 5′-end is incorporated in the RISC complex and functions as a template for 3′-untranslated region (UTR) mRNA target recognition.

The posttranscriptional gene regulation that occurs subsequent to miR-RISC recognition of mRNA has been described as either mRNA cleavage or translational repression, with the net effect of either mechanism being a reduced amount of mRNA and consequent protein (42). The degree of complementarity between miRNA and mRNA appears to determine which mechanism predominates. Perfect complementarity leads to cleavage of the mRNA through the endonucleolytic activity of the Argonaute 2 protein (Ago2) (98). Imperfect base-pairing of the miRNA with the 3′-UTR mRNA target results in translational inhibition. Critical sequences for this inhibition are thought to be nucleotides 2–8 in the 5′-end of the miRNA, the so-called seed sequence that binds specifically to the miRNA regulatory elements (MREs) in the 3′ UTR of their target mRNA (42). It is interesting that the number of base-pair matches needed between the miRNA and the target mRNA seems to differ between each target mRNA, making it difficult to identify genuine miRNA targets in silico.

Despite the large amount of evidence for the role of miRNAs in regulating the stability and translation of mRNAs, a clear quantitative understanding of this regulation is lacking. Recent studies have supported the idea that the competition for a finite number of miRNAs contributes to interactions among their targets (termed competing endogenous RNAs or ceRNAs) that could be critical for posttranslational regulation (105). The role of ceRNA implicates mRNA targets as active participants rather than passive substrates for miRNA repression. Furthermore, long noncoding RNAs, circular RNAs, and pseudogenes also contain MREs and have the potential to compete for binding to the miR-RISC complex. Thus, miRNAs appear to mediate cross talk between several ceRNAs, suggesting a large network of interactions across the transcriptome. By integrating mathematical modeling, informatics, and experimental validation, investigators recently provided a description of a ceRNA network that could predict putative outcomes after a disturbance of the network (4). These observations suggested the involvement of ceRNA–transcriptional factor interactions that influence gene expression in both physiological and pathological conditions, implicating ceRNAs as important modulators of miRNA activity and gene regulation.

The discovery that miRNAs are found in most biological fluids, including blood, urine, milk, saliva, and cerebrospinal fluid, has fostered the notion that they participate in inter- and extracellular communication (24). An interesting nutrition example is that immune-related miRNAs have been found to be plentiful in human breast milk exosomes (61). Milk exosomal miRNAs are relatively resistant to low acid pH levels like those found in the human stomach. Thus, it has been speculated that miRNA-enriched exosomes from mother's milk may target cellular mRNA translation in the infant through extracellular communication. Extracellular miRNAs have been found to

be transported in circulation by a number of different mechanisms, including membrane-derived vesicles (exosomes and microparticles), proteins, lipoproteins, and ribonucleoprotein complexes (130). Evidence suggests that some of these modes of transport involve selective cellular export mechanisms. The relative stability of extracellular miRNAs is in part due to their short length but also involves protection from circulating ribonucleases by their carriers. The Ago2 protein is an example of a carrier that provides stability for plasma miRNAs (131). In addition to withstanding ribonuclease digestion, miRNAs in various biological samples have been found to be stable in repeated freeze-thaw cycles and prolonged storage. Delivery to recipient cells and tissues is thought to occur by various processes, including direct fusion, internalization, and receptor-mediated interactions. Once delivered, these functional miRNAs are thought to utilize cellular machinery to regulate mRNA translation to protein. Thus, similar to other circulating factors, such as hormones, miRNAs may mediate communication between different cell types and participate in diverse biological processes and pathways.

CIRCULATING miRNAS AS BIOMARKERS OF DIET, NUTRITIONAL STATUS, AND DISEASE

A study in 2012 (156) reported the exciting observation that exogenous plant miRNAs were identified in the serum and tissues of mice as well as in serum from healthy Chinese men and women and that these exogenous plant miRNAs were mostly derived from dietary sources. In addition to detecting dietary plant miRNAs in animals, this report also provided evidence that a specific miRNA abundant in rice, MIR168a, regulated the expression of low-density lipoprotein receptor-associated protein-I in mouse liver. The results support the provocative notion that genetic material from food could survive the digestive tract, cross the intestinal lining to enter the bloodstream, and provide an unrecognized functional activity to regulate a gene in mammalian tissue.

Several investigations have now tried to replicate these intriguing findings. In one, it was reported that despite consumption of a vegetarian diet containing plant miRNAs, negligible expression (presented as copy number/liter of plasma) of plant miRNAs was found in mice and humans (113). This analysis suggested that the low number of copies of circulating plant miRNAs was unlikely to influence a biological signal. Interestingly, another investigator, using next-generation sequencing technology with rigorous statistical analysis, observed that a significant fraction of circulating RNA in human plasma appears to originate from exogenous species, including bacteria, fungi, and plants (139). RNAs that mapped to common cereal grains were included in these findings, suggesting that part of the RNA spectrum in the circulation is provided from food intake. In the most recent report, blood was obtained before and after feeding a miRNA-rich plant-based food source to pigtailed macaques (145). Using droplet digital polymerase chain reaction for precise, absolute nucleic acid quantification, plant and endogenous miRNAs were amplified. Although low-level amplification was observed for some plant miRNAs, amplification was variable and nonspecific, and a consistent response to dietary intake was not observed. These results do not support uptake of dietary plant miRNA, and the authors suggest that careful experiments should be performed to establish whether or not plant or other exogenous miRNAs are transferred across the gut in sufficient quantity to regulate endogenous gene targets. If circulating dietary miRNAs are found to exist in human plasma, their presence may raise the notion that the benefits of consuming a plant-based diet might be explained in part by the ingestion of plant miRNAs.

There is also evidence to suggest that miRNAs may be useful as biomarkers of nutritional status. Identification of reliable and early predictors of nutrient status is crucially needed.

Investigators used current technologies to characterize molecular signatures, including circulating miRNAs, of human zinc status in young male subjects following a dietary zinc depletion/repletion protocol (103). Nine specific serum miRNAs were downregulated in response to zinc depletion, including miR-204, miR-296-5p, and miR-375; following zinc repletion this deregulated miRNA signature was reversed. These results were of additional interest because miRNAs that were found to respond to zinc depletion were also associated with inflammation, suggesting a mechanism for zinc deficiency that contributes to cancer (103). There are suggestions that circulating miRNAs may reflect vitamin D intake or status. In one human intervention study of males, plasma miR-532-3p showed a weak correlation to serum 25-hydroxyvitamin D concentrations at baseline, but no relationship emerged following a one-year intervention of the vitamin D supplement (58). Another study found that 11 circulating miRNAs were differentially expressed among women in early pregnancy with low compared to high plasma 25-hydroxyvitamin D concentrations (30). Because of the importance of the relationship between vitamin D and health and disease, these suggestions warrant continued study in larger cohorts. Circulating miRNAs as novel candidate biomarkers for dietary nutrient status should be further explored to determine their sensitivity and specificity as indices for nutrient assessment as well as for their utility as compliance markers in dietary intervention studies.

Another aspect of great interest in the extracellular miRNA arena is that distinct circulating patterns of miRNAs appear to be altered in many diseases and conditions, including cancer and cardiovascular disease (24). This capacity suggests their potential utility as disease biomarkers and perhaps as novel therapeutic targets. Identification and validation of circulating patterns of miRNAs in subjects with varying degree of obesity and in response to weight loss by surgery is one example (92). These investigators found increased circulating levels of miR-142-3p, miR-140-5p, and miR-222 along with decreased circulating concentrations of miR-221, miR-15a, miR-520c-3p, miR-423-5p, and miR-130b with high specificity for morbid obesity. After bariatric surgery–induced weight loss in an independent cohort, modulation in the opposite direction of some of these circulating miRNAs was observed. These changes, however, were not observed in another group of subjects following diet-induced weight loss. These same investigators compared the circulating miRNA profile of lean and obese children and performed validation studies of the relevant miRNAs using a second cohort (100). The concentration of 15 circulating miRNAs was significantly associated with body mass index, percentage fat mass, waist circumference, and other clinical measures related to obesity. The authors speculated further that early detection of such aberrantly expressed circulating miRNAs and their targets may be useful as early biomarkers to identify obese children who are predisposed to future metabolic abnormalities.

In addition to their stability in various bodily fluids, circulating miRNAs offer advantages as biomarkers because they are conserved across species, their expression patterns are tissue and biological-stage specific, and they can be easily measured by quantitative polymerase chain reaction (3). Furthermore, miRNAs display many of the characteristics—sensitive, predictive, specific, robust, and noninvasive—that make them ideal biomarkers. But there are challenges, including experimental variability due to differences in sample collection, storage, RNA isolation, and accurate assessment of quantity and quality of miRNA, among other analytical factors.

miRNAS AND CANCER

Much evidence links the aberrant regulation and expression of miRNAs to the development of cancer, including their participation in critical pathways affecting tumor initiation and progression as well as their influence on the many processes associated with tumorigenesis, including proliferation, differentiation, and apoptosis (28). The first observation that miRNAs might be involved

in the development of cancer was the finding that the *miR-15/16* cluster was either deleted or downregulated in the majority of B-cell lymphomas (28). An interesting early study attempted to identify a miRNA cancer signature using 540 samples from various tissues, including lung, breast, stomach, prostate, colon, and pancreatic tumor tissues and normal tissue (135). A common miRNA expression pattern for solid cancers was identified; the pattern consisted of 36 overexpressed and 21 downregulated miRNAs, many of which were found to be protein-coding tumor suppressors and oncogenes. A systematic evaluation of several miRNA profiling studies across 20 types of cancer was recently performed. Although several caveats for miRNA as a tool in cancer prognosis were identified, such as their modest ability to distinguish clinical outcomes, the imperfect methodologies employed, and the variability of cohort size and validation approaches across studies, two miRNAs—miR-21 and let-7—emerged as the most common miRNAs associated with poor cancer outcomes (87). In addition to accurately classifying types of malignancies, miRNA signatures have also assisted with the identification of the tissue of origin for poorly differentiated tumors and for cancers that have spread to metastatic sites.

The mechanisms that have been proposed to be the cause for aberrantly expressed miRNAs in cancer cells and tissues include genetic alterations of miRNA genes, epigenetic alterations, impaired miRNA processing/biogenesis, and modulation of transcriptional regulation (51). miRNA genes have been found in fragile sites as well as other genomic regions associated with alteration in cancer, suggesting that chromosomal abnormalities and mutations are likely involved in the aberrant regulation of miRNAs in cancer (16). Another observation is the finding of miRNA copy number alterations in tumors, which accounts for diminished let-7 family expression. Focal deletion of four *let*-7 family members was observed in three cancers, including ovarian. Moreover, experimental restoration of let-7b expression reduced ovarian cancer cell growth both in vitro and in vivo (142).

Single-nucleotide polymorphisms (SNPs) in miRNA genes and miRNA target binding sites, as well as in genes involved in the biogenesis of miRNAs, may influence cancer risk (102). A recent meta-analysis supports this possibility (19). Twelve case-control studies with a total of 7,170 patients with breast cancer and 8,783 controls were utilized to determine the association of SNPs in miRNAs to breast cancer risk. It was found that miR-196a-2 rs11614913*T, miR-499 rs3746444*T, and miR-605 rs2043556*A alleles predicted a decreased risk of breast cancer among Asians but not Caucasians. An example for a polymorphism in a miRNA target binding site is for a SNP in the Kirsten rat sarcoma (*KRAS*) 3′ UTR, which was shown to diminish let-7 binding to the KRAS mRNA (88). This SNP has also been shown to be associated with increased cancer risk. Furthermore, studies have reported that deregulation of key components of miRNA biogenesis, such as Drosha or Dicer, is also associated with different cancers, and recent data suggest that SNPs in these miRNA-processing enzymes are also linked to cancer risk (102).

Aberrant miRNA expression in cancer might also be due to epigenetic changes. Reports have shown that aberrant methylation can result in aberrant miRNA expression in cancer cells (51). Investigators using the DNA methyltransferase (DNMT) inhibitor 5-aza-2′-deoxycytidine in combination with a histone deacetylase inhibitor reported global demethylation in T24 bladder cancer cells with restoration of the expression of 17 miRNAs (51). One of the regulated miRNAs, miR-127, is known to have a cytosine guanine dinucleotide island in its promoter, is silenced in several cancers, and regulates posttranscriptional expression of the oncogene B-cell lymphoma 6 protein (11). Efforts are currently underway to catalog miRNA promoter sequences and other regulatory regions in a genome-wide fashion to assist with understanding the epigenetic regulation of miRNAs (11). Furthermore, miRNAs can also regulate the expression of enzymes involved in epigenetic processes, suggesting the involvement of a controlled feedback mechanism. For example, DNMT-3A and -3B are targets of the miR-29 family (51). In fact, miR-29 translational

regulation of these DNMTs led to the reexpression of tumor suppressor genes silenced by promoter methylation in cancer.

Modulation of transcription factor activity may also regulate the expression of miRNAs in cancer development. Examples exist for tumor suppressor transcription factors [e.g., tumor protein p53 (p53) promotes the expression of the miR-34 family] and oncogenic transcription factors [e.g., v-myc avian myelocytomatosis (MYC) viral oncogene homolog induces expression of the oncogenic miR-17-92 cluster and reduces expression of tumor suppressor let-7], which supports the importance of transcription factor activity in understanding cancer development (51). Unraveling the mechanisms of the aberrant miRNA expression and function in the causation of specific cancers remains an active area of scientific inquiry.

Similar to protein-coding genes, miRNAs can be either overexpressed or underexpressed in cancer. For example, let-7a, which has been shown to act as a tumor suppressor by targeting the oncogene KRAS, is underexpressed in cancer (142), whereas miR-155, which has been shown to act as an oncogene by targeting the gene suppressor of cytokine signaling 1 (socs1), is overexpressed in several cancers (20). It should also be pointed out that whether an action is oncogenic or tumor suppressive often depends on the cellular context, as a miRNA cannot be classified as a tumor suppressor or oncogene in all circumstances. A good example has been described for the actions of miR-199a, which can either stimulate or inhibit cancer development (44).

Apparently, miRNAs may have activities in addition to transcriptional repression that are likely to influence cancer. It recently has been discovered that miRNAs are secreted by cancer cells in the surrounding tumor microenvironment within microvesicles and bind to the receptors of the toll-like receptor (TLR) family of immune cells (33). These investigators found that secreted miR-21 and miR-29 were ligands for TLR8 on immune cells, which triggered induction of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and secretion of prometastatic inflammatory cytokines. The results provide evidence for a novel miRNA link with cancer, inflammation, and immunity.

DIET, CANCER, AND miRNAS

Most studies examining the relationship between diet, miRNAs, and cancer have been performed using cancer cells in culture, and a few have been conducted in animal models of cancer. For the most part these studies are descriptive in nature, with little information about how dietary factors may influence miRNAs to give rise to the phenotypic change of the cell; these studies also fail to elucidate direct miRNA-mRNA targeting and consequent function. Examples of studies that have highlighted the relationship between dietary factors, miRNA expression, and molecular targets are listed in **Table 1**. Some of the key miRNAs found to be disrupted in cancer are also found to be responsive to dietary modulation. One review stated that a broad range of miRNA studies involving dietary factors revealed that seven miRs—let-7a, miR-21, miR-26, miR-34, miR-125, miR-146, and miR-200—are modulated by at least five dietary agents (108). When studies that also identified mRNA targets of these miRNAs are included, only let-7a, miR-21, and miR-34 are found to be modulated by at least five dietary factors that have also been shown to influence downstream targets involved in cancer pathways.

In addition to being downregulated in many cancers, the let-7 family has been found to be upregulated following exposure to dietary constituents in many cancer cells (**Table 1** and **Figure 1*a***). This modulation is associated with decreased expression of let-7 mRNA targets, including RAS and other oncogenes, as well as decreased cell growth. Another example is for the typically oncogenic miRNA miR-21, which has been shown to be downregulated by several dietary constituents in different cancer cells, resulting in upregulation of tumor suppressor protein expression, such as

Table 1 Examples of dietary modulation of miRNAs: molecular targets and biological effects

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
Let-7a	Curcumin	Up	30 μM, 12–24 hr, TE-7, TE-10 and ESO-1 cells	Notch-1, caspase-3, Bax, Bcl-2	Cell growth, apoptosis	117
	Curcumin	Up	0.5–1 μM, 48 hr, COLO-337, BxPC-3 and MIAPaCa-2 cells	Ras	Cell proliferation, colony formation	6
	Epigallocatechin gallate	Up	100 μM, 24 hr, HepG2 cells	Ras	Glucose metabolism, insulin sensitivity	129
	Green tea catechins	Up	50–200 μg/ml, 24–96 hr, NCI-H446 and MSTO-211H cells	C-myc, LIN-28	Cell proliferation	161
	Phenethyl isothiocyanate	Up	1 g/kg rat diet, 15 days after weaning, lung tissue	K-Ras	Cell proliferation, angiogenesis	52
	Retinoic acid	Up	100 nM, 4 days, NB4 cells	Ras	Cell growth	39
	Spinach	Up	10% wt/wt freeze dried spinach, 52 wk, rat colon	C-myc, Sox2, Nanog, Hnmt3b, p53	Inhibition of tumor formation	94
Let-7b	Diindolylmethane or genistein	Up	25 μM, 48 hr, L3.6 pl and Panc-1 cells			66
	Epigallocatechin gallate	Up	100 μM, 24 hr, HepG2 cells	K-Ras	Glucose metabolism, insulin sensitivity	129
Let-7c	Retinoic acid	Up	100 nM, 4 days, NB4 cells	Ras		39
Let-7d	Polyunsaturated fatty acid	Up	11.5 g fish oil/100 g diet, 10 wk post AOM, rat colon		Cytokinesis	26
	Retinoic acid	Up	100 nM, 4 days, NB4 cells	Ras		39
Let-7g	Green tea catechins	Up	50–200 μg/ml, 24–96 hr, NCI-H446 and MSTO-211H cells	C-myc, LIN-28	Cell proliferation	161
Let-7i	Curcumin	Up	0.5–1 μM, 48 hr, COLO-337, BxPC-3 and MIAPaCa-2 cells	Ras	Cell proliferation, colony formation	6
miR-7–1	Epigallocatechin or epigallocatechin gallate	Up	50 μM, 24 hr, SH-SY5Y and SK-N-DZ cells	Caspase-8, Bax, Bcl-2, AIF	Apoptosis	18

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
miR-9	Retinoic acid	Down	135 mg/kg/body weight to pregnant rats, spinal cord	Bcl-2, p53	Apoptosis, spinal cord development	159
miR-10	Protocatechuic acid	Down	1 μM, 24 hr, murine peritoneal macrophages, THP-1 cells	ABCA1, ABCG1	Cholesterol efflux	137
	Retinoic acid	Up	1 μM, 48–96 hr, SH-SY5Y cells	SFRS1	Cell differentiation, invasion, metastasis	79
mir-15	Curcumin	Up	60 μM, 24 hr, MCF-7 cells	Bcl-2	Apoptosis	150
	Curcumin	Up	5–20 μM, 24–48 hr, K562 and HL-60 cells	WT1	Cell proliferation	38
	Polyunsaturated fatty acid	Up	11.5 g fish oil/100 g diet, 10 wk post AOM, rat colon	Bcl-2, CCNE1	Apoptosis, cell cycle	26
	Retinoic acid	Up	100 nM, 4 days, NB4 cells	Bcl-2	Apoptosis	39
miR-16	Curcumin	Up	60 μM, 24 hr, MCF-7 cells	Bcl-2	Apoptosis	150
	Curcumin	Up	5–20 μM, 24–48 hr, K562 and HL-60 cells	WT1	Cell proliferation	38
	Epigallocatechin gallate	Up	100 μM, 24 hr, HepG2 cells	Bcl-2	Apoptosis	129
	Methyl-deficient diet	Down	9 and 18 wk, rat liver	Bcl-2	Apoptosis	128
miR-17	Retinoic acid	Down	10 μM, 6 days, SH-SY5Y cells	Bcl-2, MEF2D, MAPK	Cell differentiation	14
	1,25-Dihydroxy-vitamin D	Down	100 nM, 48 hr, LNCaP cells	p21, Bim, PTEN	Cell proliferation, apoptosis	140
miR-21	Curcumin	Up	2.5 and 20 μM, 24 hr, Rko and HCT116 cells	Pdcd4	G2/M cell cycle arrest, invasion, metastasis	82
	Curcumin	Down	30 μM, 12–24 hr, TE-7, TE-10 and ESO-1 cells	Notch-1, caspase-3, Bax, Bcl-2	Cell growth, apoptosis	117
	Diindolylmethane	Up	30–60 μM, 24–96 hr, MCF-7 and MDA-MB-468 cells	Cdc25A	Cell cycle arrest	56
	Epigallocatechin gallate	Down	1 mg/d, 3x/wk, 6 wk, mouse prostate cancer xenograft		Cell growth	111

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Genistein	Down	25 μM, 4 days, A-498 cells	p21, p38MAPK, cyclin E2	Cell cycle arrest, apoptosis	152
	Grape extract with resveratrol	Up	139 mg phenolics and 8 mg resveratrol/day, 1 year	TNFα, IL-1β	Inflammation	125
	Indole-3-carbinol	Down	15 wk post VC, mouse lung; 100 and 150 μM, 24 hr, A549 cells	PTEN, Pdcd4, RECK	Cell proliferation, apoptosis, and metastasis	78
	Lycopene	Up	0.05%, 8 wk, mouse liver; 25–50 μM, 24 hr, Hepa 1–6 cells	FABP7	Hepatic lipid metabolism	2
	Oleic acid	Up	50 μM, 25 hr, HepG2 cells and primary human hepatocytes	PTEN	Liver disease	134
	Resveratrol	Up	5 mg/kg/day, 21 days, rat heart	VEGF, HIF1-α	Angiogenesis	83
	Resveratrol	Down	25 μM, 24 hr, PC-3M-MM2 cells	pAkt, maspin, PDCD4	Cell viability, migration, invasiveness	109
	Retinoic acid	Up	1 μM, 6 hr, MCF7 and T47D cells	Maspin, IL1β, ICAM-1, PLAT	Inflammation, cell motility	121
	Tocotrienol	Up	5 mg/kg/day, 21 days, rat heart	VEGF, HIF1-α	Angiogenesis	83
miR-22	1,25-Dihydroxy-vitamin D	Up	100 nM, 24–96 hr, SW480-ADH and HCT116 cells	NELL2, OGN, HNRPH1, RERE, NFAT5	Cell proliferation and migration	8
miR-27a	Curcumin	Down	2.5–10 μg/ml, 16 hr, SW-480 and HT-29 cells	Sp1, Sp3, Sp4, ZBTB10	Cell growth, angiogenesis, inflammation	90
	Genistein	Down	50–200 μM, 48 hr, C918 cells	ZBTB10	Cell growth	118
	Pomegranate polyphenols	Down	2.5–10 μg/ml, 24 hr, BT474 and MB-231 cells	Sp1, Sp3, Sp4, ZBTB10	Cell growth	12
miR-29a	Ellagitannin	Up	15 μg/ml, 6 hr, HepG2 cells		Lipoprotein lipase, insulin-dependent glucose transport	144
miR-30b	Cocoa proantho-cyanidins	Down	100 mg/L, 5 hr, HepG2 cells	TGFβ, RELA, FADS2	Inflammation, NF-κB and PPAR signaling	10

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Grape seed proanthocyanidins	Down	100 mg/L, 5 hr, HepG2 cells	TGFβ, RELA, FADS2	Inflammation, NF-κB and PPAR signaling	10
miR-32	1,25-Dihydroxy-vitamin D	Up	1 nM, 48 hr, HL60 cells and 10 nM, 72 hr, U937 cells	Bim	Apoptosis	41
miR-33	Grape seed proanthocyanidins	Down	250 mg/kg body weight, ip, mouse liver; 25 mg/L, 1 hr, FAO cells	Abca1	Cholesterol efflux and transport	13
miR-34	Choline- and folate-deficient diet	Up	12 wk, mouse plasma		Liver pathology	127
	Curcumin	Up	100 nM, 72 hr, HCT116 and SW620 cells	Notch-1	Apoptosis	101
	Curcumin	Down	30 μM, 12–24 hr, TE-7, TE-10, and ESO-1 cells	Notch-1, caspase-3, Bax, Bcl-2	Cell growth, apoptosis	117
	Epigallocatechin or epigallocatechin gallate	Up	50 μM, 24 hr, SH-SY5Y and SK-N-DZ cells	Caspase-8, Bax, Bcl-2, AIF	Apoptosis	18
	Genistein	Up	60 μM, 72 hr, AsPC-1 and MiaPaCa-2 cells	Notch-1	Cell growth, apoptosis	147
	Grape extract with resveratrol	Down	139 mg phenolics and 8 mg resveratrol/day, 1 year	TNFα, IL-1β	Pancreatic cell function regulation	125
	Methyl-deficient diet	Down	9 and 18 wk, rat liver	E2F, Notch	Cell proliferation, apoptosis	128
	Selenite	Up	2.5 μM, 8 hr, LNCaP cells	p21, p53, Bax	Cell apoptosis	106
	Tocotrienol	Up	15 μM, 24–72 hr, A549 and H1650 cells	Notch-1, Hes-1, cyclin D1, survivin, Bcl-2	Proliferation, apoptosis, invasion	54
miR-92	Epigallocatechin or epigallocatechin gallate	Down	50 μM, 24 hr, SH-SY5Y and SK-N-DZ cells	Caspase-8, Bax, Bcl-2, AIF	Apoptosis	18
miR-93	Epigallocatechin or epigallocatechin gallate	Down	50 μM, 24 hr, SH-SY5Y and SK-N-DZ cells	Caspase-8, Bax, Bcl-2, AIF	Apoptosis	18

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Vitamin C	Down	1% in drinking water, 240 days, rat mammary gland; 1 mM, 48 hr, MCF-10A and T47D cells	Nrf2, NQo1, SOD3	Apoptosis, colony formation, cell migration, DNA damage	112
miR-98	1,25-Dihydroxy-vitamin D	Up	100 nM, 24 hr, LNCaP cells	LIN-28	G2/M cell cycle arrest	124
miR-99a	Epigallocatechin or epigallocatechin gallate	Up	50 μM, 24 hr, SH-SY5Y and SK-N-DZ cells	Caspase-8, Bax, Bcl-2, AIF	Apoptosis	18
miR-100	1,25-Dihydroxy-vitamin D	Up	50 nM, 24 hr, PrE, RWPE-1, RWPE-2 and LNCaP cells	E2F3, Plk1	Cell proliferation, migration	40
miR-103	Polyphenol extract *Hybiscus sabdariffa*	Up	28.6 mg/kg/day, 10 wk, liver of hyperlipidemic mice	Pank1	Triglyceride storage, acetyl-CoA metabolism	59
miR-107	Conjugated linoleic acid	Down	3 or 10 mg/day for 37 days, mouse adipose tissue	CEBPα, Cpt1b, Ucp2	Fatty acid metabolism	96
	Polyphenol extract *Hybiscus sabdariffa*	Up	28.6 mg/kg/day, 10 wk, liver of hyperlipidemic mice	Pank1	Triglyceride storage, acetyl-CoA metabolism	59
	Polyunsaturated fatty acid	Up	11.5 g fish oil/100 g diet, 10 wk post AOM, rat colon	BACE1, Serbp1	Plasminogen activation	26
miR-122	Coffee polyphenols	Up	0.5–1% for 2–15 wk, mouse liver; 2.5 μg/ml, 24 hr, Hepa 1–6 cells	SREBP, FAS	Fatty acid synthesis	91
	Copper	Up	13 mg/kg diet; 4 wk, rat liver		Liver disease	110
	Grape seed proanthocyanidins	Down	250 mg/kg body weight, ip, mouse liver; 25 mg/L, 1 hr, FAO cells	Fas	Fatty acid synthesis	13
	Licorice flavonoids	Up	20 or 100 μM, 1 hr, HepG2 cells	PTP1B	Glucose metabolism	151
	Methyl-deficient diet	Down	54 wk, rat liver		Hepatocarcinogenesis	62

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Polyphenol extract *Hybiscus sabdariffa*	Up	28.6 mg/kg/day, 10 wk, liver of hyperlipidemic mice	Fas, SREBP1	Fatty acid synthesis	59
	Quercetin	Up	2 mg/g diet, 6 wk, mouse liver	AOAH	Lipid metabolism	15
	Vitamin E–deficient diet	Down	6 months, rat liver	Bach-1, HO-1		37
miR-125	1,25-Dihydroxy-vitamin D	Up	50 nM, 24 hr, PrE, RWPE-1, RWPE-2 and LNCaP cells	E2F3, Plk1	Cell proliferation, migration	40
miR-125	Quercetin	Up	2 mg/g diet, 6 wk, mouse liver		Inflammation	15
	Vitamin E–deficient diet	Down	6 months, rat liver	TNFα	Inflammation	37
miR-126	Acai and grape polyphenols	Up	5–20 mg GAE/L, 30 min, HUVEC cells	VCAM-1	Oxidative stress, inflammation	89
miR-127	Methyl-deficient diet	Down	9 and 18 wk, rat liver	Bcl-2	Apoptosis	128
miR-128	Ginsenoside Rh2	Up	12 μg/ml, 24 hr, U251, T98MG and A172 cells	E23Fa	Cell proliferation, apoptosis	146
mir-143	Curcumin	Up	0.5–1 μM, 48 hr, COLO-337, BxPC-3 and MIAPaCa-2 cells	Ras	Cell proliferation, colony formation	6
miR-146a	Diindolylmethane	Up	25 μM, 24 hr, Colo357 and Panc-1 cells	EGFR, MTA-2, IRAK-1, NF-κB	Cell invasion	67
	Flavonol-rich fraction of yaupon holly leaves	Up	20 mg phenolics/L, 24 hr, HT-29 cells	IRAK1, TRAF6	Inflammation	91
	Retinoic acid	Down	1 μM, 4–96 hr, NB4 and 293T cells	Smad4	Cell proliferation	160
miR-151	Genistein	Down	25 μM, 4 days, LNCaP, DU145 and PC3 cells	CAZ1, IL1RAPK1, XOX17, N4BP1, ARHGDIA	Cell progression, metastasis	23
miR-155	Allyl-isothiocyanate	Down	1–10 μM, 6 hr, RAW264.7 cells; 15 mg/kg body weight/day for 7 days, mouse liver	Nrf2, HO, p65	Inflammation	136

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Grape extract with resveratrol	Down	139 mg phenolics and 8 mg resveratrol/day, 1 year	TNFα	Inflammation	125
	Isorhamnetin	Down	25–100 μM, 6 hr, RAW264.7 cells	TNFα	Inflammation	15a
	Pomegranate polyphenols	Down	2.5–10 μg/ml, 24 hr, BT474 and MB-231 cells	Akt2	Inflammation	12
	Quercetin	Down	25–100 μM, 6 hr, RAW264.7 cells	TNFα	Inflammation	15a
	Resveratrol	Down	50 μM, 14 hr, THP-1 cells and human monocytes		Inflammation	123
	Silvestrol	Down	50 nM, 24 hr, MV4-11 cells	FLT3, PU-1	Apoptosis, colony formation	5
	1,25-Dihydroxy-vitamin D	Down	20 nM, 24 hr, RAW264.7 cells	NF-κB	Inflammation, innate immunity	20
miR-181	1,25-Dihydroxy-vitamin D	Down	1 nM, 48 hr, HL60 cells and 10 nM, 72 hr, U937 cells	p27, CD14, CD11b	G1 cell cycle arrest	141
	Grape extract with resveratrol	Up	139 mg phenolics and 8 mg resveratrol/day, 1 year	TNFα, IL-1β	Inflammation	125
miR-182	25-Hydroxyvitamin D	Down	250 nM, 24 hr, 7 days, MCF12A cells	Cyclin D, Bcl-2, caspase-2	Cell proliferation, apoptosis	97
miR-186	Curcumin	Down	15 μM, 48 hr, A549 cells	Caspase-10	Apoptosis	154
miR-199	Curcumin	Down	5 mg/day, 4 wk, mouse liver treated with CCL4	MMP-13, TIMP-1	Liver fibrosis	48
miR-200	Curcumin	Down	5 mg/day, 4 wk, mouse liver treated with CCL4	MMP-13, TIMP-1	Liver fibrosis	48
	Curcumin	Up	0.5–1 μM, 24 hr, MIAPaCa-2 and BxPC-3 cells	PTEN, MMP	Colony formation, wound healing	114
	Diindolylmethane	Up	25 μM, 24 hr, MIAPaCa-2 and BxPC-3 cells	PTEN, MMP	Colony formation, wound healing	114

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
	Diindolylmethane	Up	25 μM, 48 hr, L3.6 pl and Panc-1 cells	ZEB1, slug and vimentin	Reversal of epithelial-to-mesenchymal transition	66
	Genistein	Up	25 μM, 48 hr, L3.6 pl and Panc-1 cells	ZEB1, slug and vimentin	Reversal of epithelial-to-mesenchymal transition	66
	Methyl-deficient diet	Down	9 and 18 wk, rat liver	ZFHX1B	Liver fibrinogenesis, epithelial-to-mesenchymal transition	128
miR-203	Curcumin	Up	10 μM, 3 days, T24 cells	Akt2, Src	Proliferation and apoptosis	104
miR-210	Epigallocatechin gallate	Up	40 μM, 1–9 hr, CL13 cells	Stabilization of HIF-1α	Proliferation and anchorage-independent growth	138
miR-222	Conjugated linoleic acid	Down	3 or 10 mg/day for 37 days, mouse adipose tissue	GLUT4, PPARγ, Fasn, Ucp2, TNFα	Adipogenesis	96
	Folate deficiency	Up	5 days, TK-6 cells; human blood from top or bottom 1% of folate status			75
	Genistein	Down	50 μM, 96 hr, PC-3 cells	ARHI	Cell proliferation	21
miR-223	Ellagitannin	Down	15 μg/ml, 6 hr, HepG2 cells			144
miR-302	Folate deficiency	Down	4 days, mouse embryonic stem cells	Lats2, caspase-3	G1/G0 cell cycle arrest, apoptosis	68
	Western-type diet	Down	LDL receptor knockout mice, 2 wk, mouse liver	ABCA1, ELOVL6	Hepatic cholesterol, fatty acid, and glucose metabolism	50
miR-330	Epigallocatechin gallate	Up	1 mg/d, 3x/wk, 6 wk, mouse prostate cancer xenograft		Apoptosis	111
miR-370	Ellagitannin	Down	15 μg/ml, 6 hr, HepG2 cells		Fatty acid oxidation	144
miR-378	Fisetin	Down	0.05% w/w in 20% fat diet, 10 wk, mouse liver	SREBP-1, SCD1, FASN, PGC-1β, NRF-1	Fatty acid oxidation, lipogenesis	53
miR-467b	High-fat diet	Down	20% lard diet, 8 wk, mouse liver	LPL	Insulin resistance	1

(*Continued*)

Table 1 (*Continued*)

miRNA	Dietary component	Up- or down-regulation	Experimental conditions	Molecular targets	Biological effects	Reference
miR-498	1,25-Dihydroxy-vitamin D	Up	100 nM, 6 days, OVCAR3 cells	Telomerase	Cell growth	60
miR-574	Genistein	Up	25–50 μM,4 days, DU145 and PC3 cells	RAC1, EGFR, EP300	Cell proliferation, migration, and invasion	22
miR-622	Resveratrol	Up	12.5–50 μM, 48 hr, 16HBE-T and H460 cells	K-Ras, cyclin D2, c-myc	Cell proliferation	47
miR-627	1,25-Dihydroxy-vitamin D	Up	100 nM, 24 hr, HT-29 and HCT-116 cells	JMJD1A	Cell proliferation, xenograft growth	93
miR-637	1,25-Dihydroxy-vitamin D	Up	10 nM, 6 hr, primary human osteoblasts and MG-63 cells	DAPK3, COL4A1, osteocalcin	Cell differentiation	69
miR-663	Resveratrol	Up	50 μM, 14 hr, THP-1 cells and human monocytes	JunB, JunD	AP-1 activity, immune response	123
	Retinoic acid	Up	0.1 μM, 24–72 hr, HL-60 cells	CD11b	Cell proliferation, differentiation	55
miR-1228	1,25-Dihydroxy-vitamin D	Up	10 nM, 6 hr, primary human osteoblasts and MG-63 cells	LRP1, BMP2K, osteopontin	Cell differentiation	69
miR-1260b	Genistein	Down	25 μM, 4 days, A-498 and Caki-2 cells	sFRO1, Dkk2, Smad4	Cell apoptosis, proliferation, invasion	49
miR-1296	Genistein	Up	25–50 μM, 24 hr, PC3 cells	MCM2	Cell proliferation	73

Abbreviations: ABC, ATP-binding cassette; AIF, apoptosis-inducing factor; ARHI, adrenodoxin reductase homolog I; BMP2K, bone morphogenetic protein-2 inducible kinase; CD, cluster of differentiation; COL4A1, collagen, type IV, alpha 1; COX, cyclooxygenase; DAPK, death-associated protein K; Dkk2, Dickkopf homolog 2; EGFR, epidermal growth factor receptor; ELOVL6, elongation of long-chain fatty acids family member 6; EP300, E1A binding protein p300; FASN, fatty acid synthase; GLUT4, glucose transporter type 4; HIF, hypoxia-inducible factor; IL-1β, interleukin 1β; ip, intraperitoneal; JMJD1A, jumonji domain containing 1A; K-Ras, Kirsten rat sarcoma; LPL, lipoprotein lipase; LRP, lipoprotein receptor; MCM, mini-chromosome maintenance protein; MMP, matrix metalloproteinase 2; NF-κB, nuclear factor κB; NRF, nuclear factor (erythroid-related); PGC-1β, peroxisome proliferator-activated receptor γ coactivator 1β; PPAR, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homolog; SCD1, stearoyl-CoA desaturase 1; SFR, splicing regulatory factor; Sox2, sex-determining region Y (SRY)-box 2; SREBP, sterol regulatory element–binding protein; TNF, tumor necrosis factor; UCP, uncoupling protein; VEGF, vascular endothelial growth factor; ZEB, zinc finger E-box-binding homeobox; ZFHX, zinc finger homeobox.

phosphatase and tensin homolog (PTEN) and p21, and a less tumorigenic phenotype (**Table 1**). There are, however, examples in which miR-21 is upregulated by dietary factors, as is the case for 3,3′-diindolylmethane in breast cancer cells (56; **Table 1**). In this context miR-21 was not oncogenic in activity because it was associated with the downregulation of cell division cycle 25A protein and cell cycle arrest.

A few studies go beyond descriptive observations and attempt to determine how dietary constituents regulate miRNA expression in cancer cells. In this regard, the *prelet-7a-2* gene was recently shown to be regulated by a vitamin D response element (VDRE) (45). Chromatin immunoprecipitation and other experiments demonstrated that the 1,25(OH)2D3/vitamin D receptor (VD3/VDR) could interact with a VDRE upstream of the *prelet-7a-2* gene to turn on gene expression. These results suggest that modulation of transcription factor activity is one way in which dietary factors, in particular the let-7 family as shown in **Figure 1*b***, may increase miR expression.

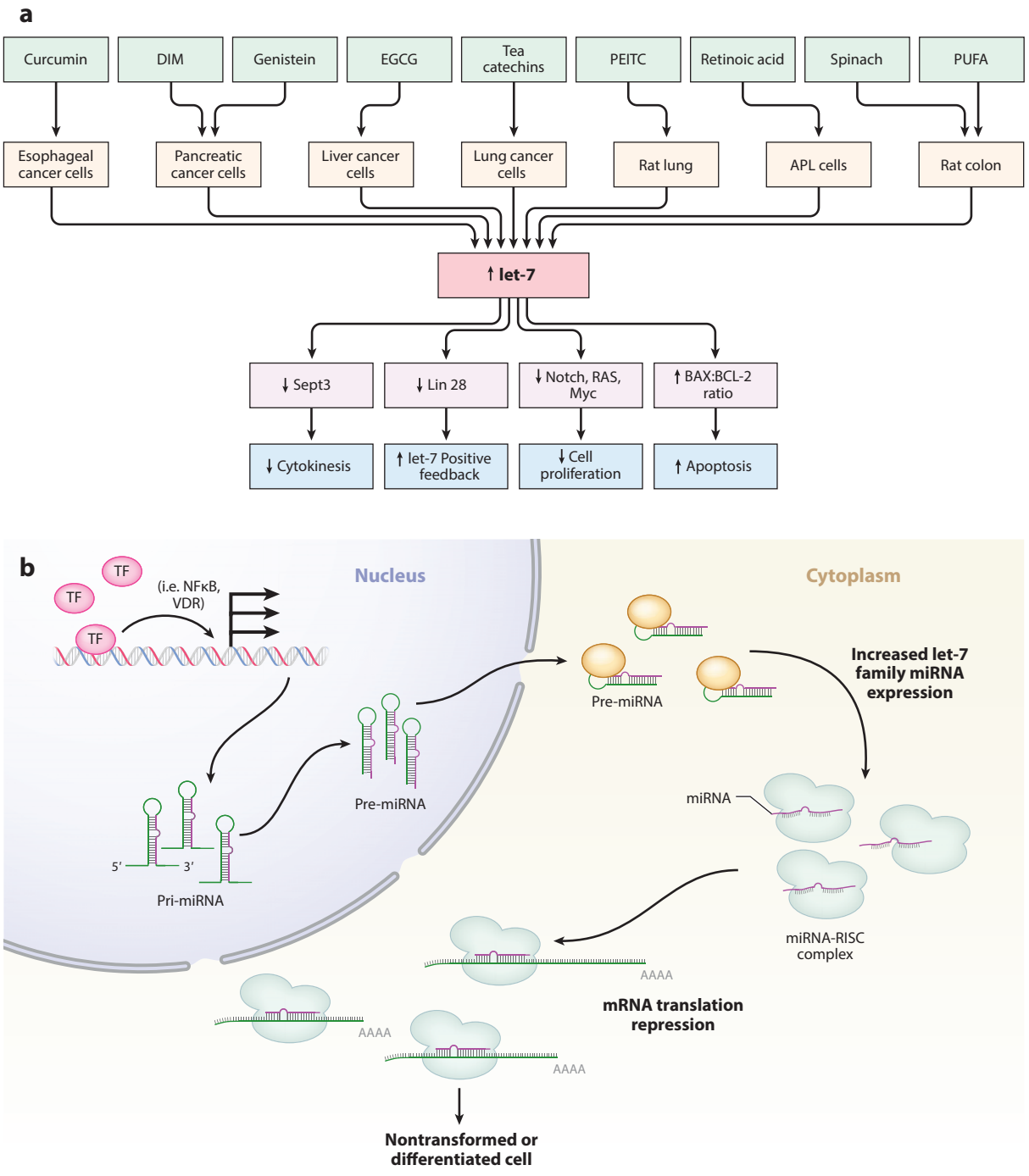
Epigenetic modulation by dietary factors might be another way to regulate miRNA expression in cancer cells. A soy isoflavone extract (20 μM) was found to demethylate the DNA promoter sequence of miR-29a and miR-1256 in prostate cancer cells (65). This DNA demethylation was associated with increased expression of miR-29a and miR-1256 as well as decreased expression of their mRNA targets, tripartite motif-containing 68 protein and phosphoglycerate kinase 1, and inhibition of prostate cancer cell growth and invasion.

Dietary factors may also influence expression and activity of components of the miRNA biogenesis pathway in cancer. For example, resveratrol (50 μM) transcriptionally induced the expression of Ago2 in breast cancer cells, which was observed to increase tumor-suppressive miRNAs and induce long-term gene-silencing response in these cells (46). These activities were associated with diminished viability and invasion of these cancer cells. In a recent report, long-term dietary feeding of grape seed extract (0.25% or 0.5% w/w) was found to decrease carcinogen-induced colon tumorigenesis in A/J mice, possibly through modulating miRNA expression by inducing Ago2 expression (27). These findings link the ability of dietary constituents to modulate miRNA expression through the regulation of miRNA processing machinery.

Few studies of the relationship between diet, miRNAs, and cancer have been able to implicate miRNAs directly in the dietary-protective effect. A recent example involves miR-21, which was found to be overexpressed in breast cancer cells contributing to growth and metastasis through colony-stimulating factor-1 (CSF-1) mRNA regulation (74). Treatment of these breast cancer cells with docosahexaenoic acid, which is found in fish oil, inhibited miR-21 expression, resulting in increased PTEN, which negatively regulated the transcription of CSF-1. Transfection of miR-21 into breast cancer cells demonstrated that more miR-21 prevented the docosahexaenoic acid–induced downregulation of CSF-1 expression, whereas utilizing a miR-21 sponge or miR-21 inhibitor markedly decreased CSF-1 in these breast cancer cells. Studies utilizing miRNA transgenes and miRNA sponges and other positive and negative functional controls are necessary to determine direct functional activity of miRNAs in response to dietary constituents.

More mechanistic in vivo studies are needed to determine functional effects of miRNAs on the diet and cancer relationship. By comparing mice with active epidermal growth factor receptors (EGFRwt) to mice with nonfunctional EGFR (EGFRwa2) in colon carcinogenesis experiments, investigators were able to show that tumor promotion by a Western diet (20% fat versus 5% fat for standard diet) required active EGFR signals in the EGFRwt animals (162). Furthermore, they found that expression of miR-143 and miR-145 was decreased in EGFRwt colon tumors, whereas expression was increased in colon tumors of EGFRwa2 mice. They concluded from their observations that a Western diet reduced the expression of the tumor suppressors miR-143 and miR-145 through EGFR signaling, which was associated with upregulation of MYC and KRAS, among other oncogenes, resulting in enhanced tumorigenesis. These investigators also found that miR-143 and miR-145 were reduced in human sporadic and ulcerative colitis–associated colon cancers.

An emerging approach for the study of the relationship between diet, miRNAs, and cancer is the use of systems biology techniques complemented with experimental validation. In one such study, investigators found that the let-7/MYC/Lin28 axis was deregulated in heterocyclic amine–induced colon carcinogenesis in rats (94). In a dietary prevention arm of the study, it was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found that the tumor-suppressive effects of dietary spinach correlated with elevated levels of let-7 family members and partial reversion to normal of many of the deregulated let-7 mRNA targets, including MYC, sex-determining region Y (SRY)-box 2 (Sox2), Nanog homeobox (Nanog), and p53. These results further highlight the possible role of dietary regulation of the let-7 family, which are important tumor suppressor miRNAs that warrant continued study.

Findings from human studies concerning the relationship between diet, miRNAs, and cancer are emerging. In one study, the effects of a 12-month low-glycemic-load (15% reduction from baseline diet) dietary intervention on serum miRNA expression and mRNA targets of specific miRNAs were determined in premenopausal women at risk for breast cancer (defined by mammographic density) (77). Twenty miRNAs were found to be differentially expressed after the low-glycemic-load diet intervention compared to baseline. The most strongly upregulated miRNA was let-7b, and the most strongly downregulated was miR-623. The differentially expressed miRNAs were predicted to influence mRNA targets associated with energy balance and cancer pathways. The results point to the gene-regulatory effects of diet on cancer pathways.

Another human clinical study examined the association between the dietary intake of the flavonoid quercetin and miRNA expression in lung tumor tissue (63). Intake of quercetin-rich foods was determined from food frequency questionnaire data of 264 patients with lung cancer (144 patients with adenocarcinoma and 120 with squamous cell carcinoma) for whom lung tumor tissue miRNA expression data were also obtained (63). A quercetin-rich diet was associated with differential expression of miRNAs in lung tumor tissue. Interestingly, the expression of miRNAs in the let-7 family was strongly associated with more frequent consumption of quercetin-rich foods. Although this study did not link these findings to any lung cancer outcome, it was suggested that the findings may help to explain the association between quercetin-rich food consumption and reduced lung cancer risk that has been observed in many epidemiological studies.

The possibility that SNPs in miRNA genes explain the association between diet and cancer risk has also been recently studied. A suggestion of an association between the presence of the has-miR-149 rs2292832 SNP (CT + CC versus TT) and gastric cancer risk in Chinese males was recently reported (157). It was also found that tea drinking showed a protective effect on gastric cancer risk in this cohort. Most interesting was the finding that tea drinking was protective for gastric cancer among has-miR-149 CT + CC carriers. These results warrant follow-up in large cohorts to determine if miRNA gene–nutrient interactions are important contributors to cancer risk and prevention.

miRNA AND CARDIOVASCULAR DISEASE

The main underlying cause of cardiovascular disease, atherosclerosis, is an inflammatory disease characterized by endothelial activation and accumulation of lipid in infiltrated macrophages, which

Figure 1

Dietary modulation of the let-7 family of microRNAs (miRNAs) in cancer. (*a*) Dietary exposure of several different factors has been shown to be associated with increased let-7 expression, which decreases expression of let-7 messenger RNA (mRNA) targets, including RAS and other oncogenes, resulting in decreased cell proliferation. (*b*) Modulation of transcription factor activity is one mechanism whereby dietary factors are thought to increase miR expression. For example, increased vitamin D binding to its receptor (VDR) may enhance the expression of a let-7 gene through binding of a vitamin D response element in the gene. Abbreviations: APL, acute promyelocytic leukemia; BAX, bcl-2-like protein 4; BCL-2, B-cell lymphoma 2; DIM, 3,3′-diindolylmethane; EGCG, epigallocatechin gallate; Lin 28, lin-28 homolog A; Myc, v-myc avian myelocytomatosis viral oncogene homolog; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PEITC, phenethyl isothiocyanate; PUFA, polyunsaturated fatty acid; RAS, rat sarcoma; RISC, RNA-induced silencing complex; Sept3, septin 3; TF, transcription factor; VDR, vitamin D receptor.

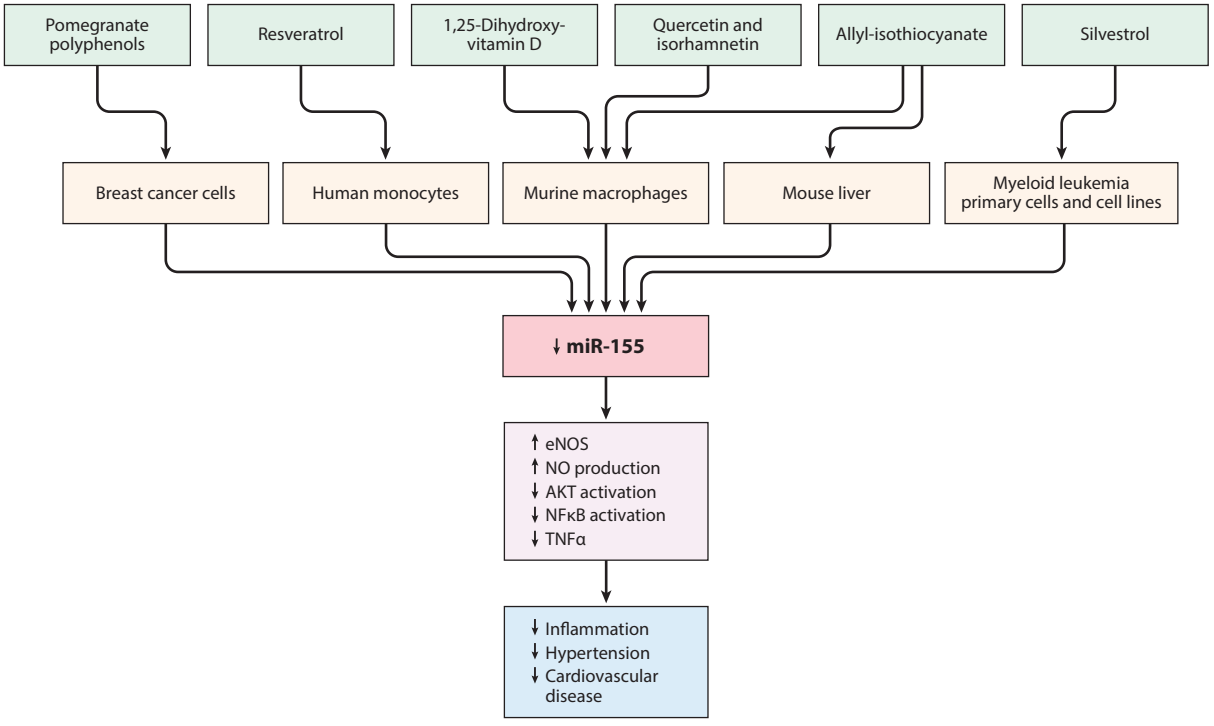

Figure 2

Dietary regulation of the inflammatory-associated miR-155. Many different dietary components downregulate miR-155 expression in several contexts (breast cancer cells, human monocytes, murine macrophages, mouse liver, myeloid leukemia cells); downregulated miR-155 expression is associated with reduced inflammation, reduced hypertension, and reduced cardiovascular disease. Abbreviations: AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; TNFα, tumor necrosis factor alpha.

starts the process of plaque formation and narrowing of the vessel lumen. miR-155 has been linked to several vital inflammatory signal cascades involved in atherosclerosis in different cell types including endothelial cells, vascular smooth muscle cells, dendritic cells, and macrophages (71). miR-155 can modulate the expression of genes correlated with inflammation in various cell types in vitro and can modulate atherogenesis in vivo (71). Other miRNAs involved in atherosclerosis include miR-145, which controls differentiation of smooth muscle cells and promotes lesion formation, and miR-136, which signals the need for endothelial repair when it is transferred from apoptotic endothelial cells in microvesicles (143).

Concentrations of miR-155 in serum have been proposed as a biomarker of cardiovascular disease because they are significantly downregulated in patients with coronary artery disease as compared to controls (25). Many different dietary components have been shown to modulate miR-155 expression (**Table 1**, **Figure 2**). Long-term supplementation with a grape extract containing resveratrol for 12 months downregulated miR-155 expression in peripheral blood mononuclear cells of hypertensive patients with coronary artery disease and was associated with the regulation of NF-κB and TLR signaling as well as the expression of tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL1β) (125).

Dietary resveratrol has also been shown to modulate miRNAs associated with ischemia/reperfusion and cardiac hypertrophy. Ischemia/reperfusion of rat myocardium leads to differential

expression of over 50 miRNAs. However, rats pretreated with 5 mg resveratrol/kg/day for three weeks had significant protection against ischemia/reperfusion injury, which was associated with altered expression of 25 miRNAs (84). Resveratrol-regulated miRNAs in ischemia/reperfusion include miR-21, miR-20b, miR-27a, and miR-9. These miRNAs have been previously shown to regulate the extracellular signal–regulated kinase/mitogen-activated protein kinase signaling pathway in cardiac fibroblasts (miR-21), to modulate vascular endothelial growth factor and angiogenesis through hypoxia-inducible factor 1 alpha (HIF-1α) (miR-20b), or to regulate forkhead box protein O1 (miR-27a) and sirtuin 1 (miR-9) (85). Resveratrol also reduces cardiac hypertrophy in hypertensive animals via upregulation of miR-27a and altered cellular signaling including the protein kinase B/phosphoinositide 3-kinase pathway (64). These results demonstrate the pleiotropic effects of dietary components such as resveratrol as well as the multiple miRNAs that can be modulated and their diverse cellular targets.

miRNA AND TYPE 2 DIABETES MELLITUS

Type 2 diabetes is characterized by chronic elevation of blood glucose concentrations and resistance to insulin and is one of the major risk factors for cardiovascular disease. Diabetic patients have a unique plasma miRNA signature including decreased levels of miR-126, miR-15a, miR-29b, and miR-223 and increased levels of miR-28-3p (153). Of note, altered expression of several miRNAs is detectable years before the manifestation of diabetes.

miR-375, which is highly expressed in pancreatic islet cells, is required for normal glucose homeostasis. miR-375 expression is elevated in the pancreatic islets of *ob/ob* diabetic mice (99). Knockdown of miR-375 in these mice results in hyperglycemia, increased fasting and fed plasma glucagon concentrations, and increased gluconeogenesis and hepatic glucose output. Furthermore, pancreatic β cell mass is decreased in miR-375 knockout mice as a result of impaired proliferation (99). In humans, autopsy data have also revealed upregulated pancreatic tissue miRNA-375 in diabetic patients that correlated positively with the frequency and the severity of islet amyloid formation and negatively with islet β cells (158). These data suggest that deregulation of miR-375 may be a compensatory mechanism in diabetes to increase β cell mass to counteract increased peripheral insulin resistance.

Although the let-7 tumor suppressor miRNA is known for its role in carcinogenesis, altered expression of let-7 also plays a role in diabetes. Transgenic mice that overexpress let-7 have insulin resistance and impaired glucose tolerance, which are mediated through the let-7-facilitated inhibition of multiple components of the insulin-phosphatidylinositide 3 kinase/mammalian target of rapamycin pathway, including insulin-like growth factor 1 receptor, insulin receptor, and insulin receptor substrate 2 (163). Moreover, anti-miR-induced knockdown of let-7 is sufficient to treat obesity-induced glucose intolerance via the restoration of insulin signaling in muscle and liver (35). In addition, Zhu et al. (163) demonstrated in large-scale genome-wide association studies that multiple let-7 targets are associated with type II diabetes, suggesting a potential role for aberrant regulation of let-7 target genes in diabetes. As has already been mentioned (**Table 1**, **Figure 1**), many dietary components can influence let-7 expression.

miRNA IN ADIPOGENESIS AND OBESITY

Obesity, which is characterized by increased fat mass and energy storage in adipose tissue, is a nationwide epidemic that is related to diseases such as type 2 diabetes, cardiovascular disease, and cancer. miRNAs are important regulators of the development and function of both white and brown adipose tissue differentiation and biology. miRNAs modulate not only mass size but also the metabolic consequences of obesity and adipose tissue metabolism. Interestingly, a set of

miRNAs (including miR-103, miR-107, and miR-143) are induced during adipogenesis (which may accelerate fat cell development) but then are downregulated in the obese state (148). These observations have important implications for understanding adipose tissue deregulation in obese mice and humans as well as the link between insulin and chronic inflammation and obesity (148). In addition to altered adipocyte miRNA expression during obesity, there is an altered expression of miRNAs in the circulation (92) and peripheral blood mononuclear cells (80). Moreover, the basal expression of certain miRNAs in blood cells can differentiate between responders and nonresponders (miR-935, miR-4772, miR-223, and miR-376b) to diet-induced weight loss (80).

Peroxisome proliferator-activated receptor γ coactivator 1β (PGC-1β) is a transcriptional factor that regulates metabolism and mitochondrial biogenesis through stimulation of nuclear hormone receptors and other transcription factors (17). Embedded in this gene are two miRNAs, miR-378 and miR-378*, which counteract the metabolic actions of PGC-1β. Mice genetically lacking miR-378 and miR-378* (while leaving the host gene *Pgargc1b* intact) are resistant to high-fat-diet-induced obesity and exhibit enhanced mitochondrial fatty acid metabolism and elevated oxidative capacity of insulin target tissues (17). Dietary fisetin, a naturally occurring flavonol that is widely distributed in fruits and vegetables, can protect against hepatic fat accumulation in mice fed a high-fat diet via inhibition of miR-378 expression (53). These observations may partially explain how a healthy lifestyle, such as a diet high in fruits and vegetables, may be protective against some of the consequences of obesity.

miR-143 was the first miRNA identified that is associated with the regulation of adipocyte differentiation. Differentiating adipocytes have increased expression of miR-143, and treatment with antisense oligonucleotides against miR-143 inhibits human cultured adipocyte differentiation and leads to a decrease in triglyceride accumulation and the downregulation of peroxisome proliferator-activated receptor-gamma 2 (PPARγ2), adipocyte fatty acid binding protein, and glucose transporter type 4 (32). Mice fed a high-fat diet have increased miR-143 expression in their mesenteric fat, which is associated with elevated body and mesenteric fat weight as well as with markers of adipocyte differentiation such as PPARγ (119). miR-143 is also upregulated in the liver of genetic mouse models of obesity; transgenic overexpression of miR-143 impairs insulin-stimulated AKT kinase activation and glucose homeostasis; and mice deficient in miR-143 are protected from the development of obesity-associated insulin resistance (57).

miR-103 and miR-107 have also been associated with obesity. The expression of miR-103 and miR-107 is elevated in the liver of both leptin-deficient (*ob/ob*) and diet-induced rodent models of obesity (95). Overexpression or knockdown of miR-107 in murine hepatic cells demonstrated that the expression of its putative target, fatty acid synthase, was dramatically decreased or increased, respectively (95). Because miR-103 and miR-107 differ by only one nucleotide 3′ in their seed region and constitute a miRNA family, they can be knocked out simultaneously. Pharmacologic inhibition of miR-103/107 with an antagomir against miR-103 improved glucose homeostasis in obese mice, reduced adipocyte size, and decreased overall fat mass (126). Mice treated with dietary conjugated linoleic acid had decreased expression of miR-103/107, which correlated with genes involved in fatty acid metabolism (96). Similarly, polyphenols derived from the plant *Hibiscus sabdariffa* inhibited the expression of miR-103/107 in hyperlipidemic mice, which was associated with changes in lipid and glucose metabolism (59). If these associations are confirmed in nonhuman primates and humans, it would suggest that miR-103/107 may represent therapeutic targets against obesity and its related metabolic alterations.

miRNAS IN NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive fat accumulation in the liver (steatosis) without any other evident cause (such as viral infections) of chronic liver disease.

NAFLD may appear as just steatosis, or as a more severe form may develop into nonalcoholic steatohepatitis. NAFLD is closely associated with obesity, insulin resistance, and hyperlipidemia and increases the risk of cardiovascular disease, type 2 diabetes, and liver-related complications. In mice, plasma miRNAs (miR-34a, miR-122, miR-181a, miR-192, and miR-200b) are sensitive indicators of interstrain differences in the severity of liver injury induced by a choline- and folate-deficient diet, with the strongest correlation occurring with miR-34a (127). Serum concentrations of miR-21, miR-34a, miR-122, and miR-451 are higher in patients with NAFLD than in controls (149). Moreover, the serum levels of miR-122 correlate with the severity of liver steatosis (149). In contrast, a recent molecular analysis of the liver of rats with diet-induced NAFLD found decreased expression of miR-21, miR-122, and miR-451 but increased miR-34a (7). These contrasting results suggest that either the serum levels of miR-21, miR-122, and miR-451, but not miR-34a, are inversely associated with their hepatic expression or that the same miRNAs have different expression profiles during disease pathogenesis in different species. Thus, the association between hepatocyte and serum miRNA expression requires further research.

Many different animal studies suggest a relationship between hepatic miR-122 and NAFLD. miR-122 is the most abundant miR in the liver, accounting for more than 80% of total miR content in this organ (72). miR-122 inhibition in a diet-induced obesity mouse model resulted in decreased plasma cholesterol levels and a significant improvement in liver steatosis, accompanied by reductions in several lipogenic genes, such as 3-hydroxy-3-methylglutaryl-CoA synthase 1, dehydrocholesterol reductase, and squalene epoxide (31). Similarly, silencing miR-122 in chimpanzees and African green monkeys reduced total plasma cholesterol levels (29). Many different dietary components can modulate miR-122 expression (**Figure 3**). Polyphenol extracts from *H. sabdariffa* (59), quercetin (15), and coffee (86) prevent diet-induced liver steatosis in mice through the upregulation of miR-122 (**Figure 3**). In contrast, a vitamin E-deficient diet (37) or a folate-, methionine-, and choline-deficient diet (62) downregulates miR-122 and increases liver damage. These data suggest that dietary modulation of hepatic miR-122 expression may influence the development of NAFLD through modulation of miR-122.

Hepatic miR-21 is also decreased during steatosis in a mouse model of diet-induced obesity and in Hepa 1–6 cells treated with stearic acid and is associated with upregulation of fatty-acid binding protein 7 (2). Dietary lycopene improved hepatic steatosis in high-fat-fed mice and reduced intracellular lipid accumulation induced by stearic acid in the cells (2). Future studies should investigate the role of lycopene for preventing NAFLD in humans.

FUTURE DIRECTION AND CONCLUSIONS

miRNAs are small noncoding RNAs that regulate protein production through interaction with the 3′-UTRs of target mRNAs of protein-coding genes, resulting in inhibition of mRNA translation or degradation of the mRNA transcript. A current focus, as well as a challenge, for miRNA studies is to identify the downstream targets and signaling pathways that miRNAs regulate. Much of this work has provided new insights into the role of miRNA in various biological events, including disease pathogenesis. Emerging topics concerning the biology of miRNA include the influence of RNA-binding proteins on miRNA biogenesis, activity, and stability, the capability of competing endogenous RNAs to regulate miRNA function, and the role of circulating miRNAs as putative intercellular signaling molecules and as biomarkers of health and disease. Advances in these and other areas, including the influence of nutritional exposures on the regulation of miRNA, are likely to provide additional molecular insights about the development and prevention of chronic diseases. Many of the studies on dietary modulation of miRNA that have been published and that are discussed in this review are descriptive, i.e., cells or animals are treated with a dietary

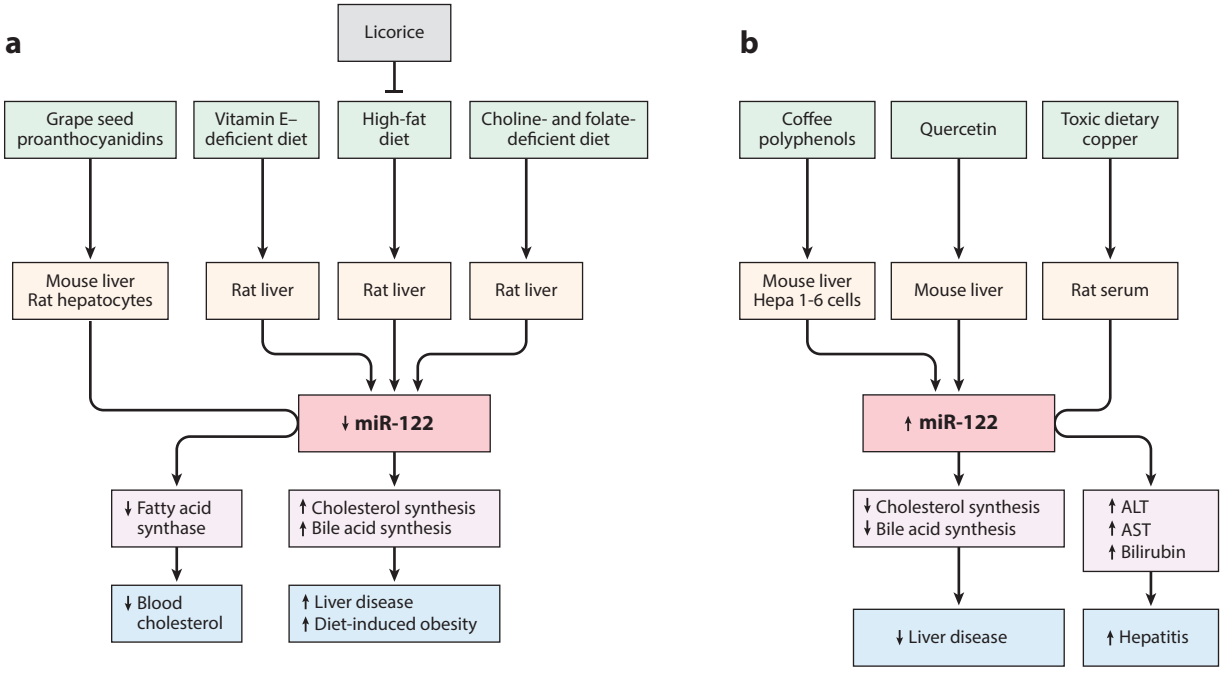

Figure 3

Dietary components modulate miR-122 expression to alter liver function. (*a*) Dietary factors (vitamin E–deficient diet, high-fat diet, choline- and folate-deficient diet) downregulate hepatic miR-122, which is associated with the development of liver disease. Grape seed proanthocyanidins also downregulate hepatic miR-122, but this is associated with a favorable outcome on blood cholesterol levels. (*b*) Dietary components (coffee polyphenols, quercetin) upregulate hepatic miR-122, which is associated with a reduction in liver disease. Toxic levels of dietary copper also upregulate hepatic miR-122, but this is associated with increased hepatitis. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

factor, and miRNA expression and downstream target protein expression are measured. Thus, there is a need for experimental functional studies that use both cells in culture and animal models to explicate the intricate regulation of miRNAs and their targets and how dietary factors may participate in these processes. The use of transgenic mice with specific loss or gain of miRNA function may be helpful in deciphering specific actions. Performing human controlled feeding studies that examine molecular features such as circulating miRNA expression—perhaps in the context of a systems biology approach—in response to foods, food constituents, or dietary patterns will help to advance an understanding of the relevance of miRNA expression for health promotion and disease prevention.

The results of cell culture studies must be interpreted carefully and with particular attention to concentrations used and the timing of dietary factor exposure. Studies should state the basis for concentrations and timing of exposure to the dietary factor so that physiological relevance can be ascertained. For studies in animals, the frequency of dietary exposure needed to sustain a miRNA response as well as considerations about the bioavailability and metabolism of the dietary constituent may also need to be explored. More studies are needed to determine the appropriate timing of dietary exposure that is critical for maintaining physiological miRNA expression for health maintenance and disease prevention or to disrupt or reverse aberrant miRNA expression during early stages of disease development. The importance of the temporal influence of diet is highlighted by recent animal studies that have examined the effects of in utero exposure on miRNA

expression and function in offspring. In one study, a maternal high-fat diet during pregnancy and lactation was found to alter the hepatic expression of miRNAs and genes involved in metabolism in the adult offspring (155). Among the changes in these offspring were increased hepatic mRNA levels of insulin-like growth factor 2 and reduced expression of let-7c. Such changes may influence the response to dietary and other challenges in adult life. Another study suggested that paternal obesity, induced by a high-fat diet, influenced multigenerational transmission of obesity and metabolic disturbances to offspring, in part through aberrant sperm miRNA expression (36). How diet influences miRNA expression through the life span and in different physiological contexts requires further study.

Much remains to be discovered regarding dietary modulation of miRNA expression, including cell- or tissue-specific responses, the quantity of the dietary constituent or type of dietary pattern needed to bring about the desired biological effect, and the timing and duration of exposure. Other variables that can influence the response include interactions between genetic, epigenetic, and microbial influences. The great interest in the role of the microbiome in health and disease has some in the field speculating that bacterial small RNAs may influence mammalian gene expression or that mammalian miRNAs may influence the microbiome, but currently evidence does not exist for these relationships. Furthermore, interactions between dietary factors and miRNA gene variants may be informative for identifying disease risk in subgroups and may explain variation in response to diet. Moreover, circulating miRNAs may be useful as biomarkers of disease, susceptibility to disease, or nutritional status. It would be difficult to argue that overall diet and dietary patterns do not influence health and disease, but there is only limited evidence from randomized controlled trials that dietary factor supplementation may prevent chronic disease. Unraveling how diet and dietary factors influence molecular mechanisms such as miRNA expression and function will likely contribute to our understanding of chronic disease prevention in the broader sense.

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LITERATURE CITED

1. Ahn J, Lee H, Chung CH, Ha T. 2011. High fat diet induced downregulation of microRNA-467b increased lipoprotein lipase in hepatic steatosis. *Biochem. Biophys. Res. Comm.* 414:664–69
2. Ahn J, Lee H, Jung CH, Ha T. 2012. Lycopene inhibits hepatic steatosis via microRNA-21-induced downregulation of fatty acid-binding protein 7 in mice fed a high fat diet. *Mol. Nutr. Food Res.* 56:1665–74
3. Ajit SK. 2012. Circulating microRNAs as biomarkers, therapeutic targets, and signaling molecules. *Sensors* (*Basel*) 12:3359–69
4. Ala U, Karreth FA, Bosia C, Pagnani A, Taulli R, et al. 2013. Integrated transcriptional and competitive endogenous RNA networks are cross-regulated in permissive molecular environments. *Proc. Natl. Acad. Sci. USA* 110:7154–59
5. Alachkar H, Santhanam R, Harb JG, Lucas DM, Oaks JJ, et al. 2013. Silvestrol exhibits significant in vivo and in vitro antileukemic activities and inhibits FLT3 and miR-155 expression in acute myeloid leukemia. *J. Hematol. Oncol.* 6:21–33
6. Ali S, Ahman A, Abouukameel A, Bao B, Padhye S, et al. 2012. Increased RAS GTPase activity is regulated by miRNAs that can be attenuated by CDF treatment in pancreatic cancer cells. *Cancer Lett.* 319:173–81
7. Allisi A, Da Sacco L, Bruscalupi G, Piemonte F, Panera N, et al. 2011. miRNome analysis reveals novel molecular determinants in the pathogenesis of diet-induced nonalcoholic fatty liver disease. *Lab. Invest.* 91:283–93

8. Alvarez-Díaz S, Valle N, Ferrer-Mayorga G, Lombardía L, Herrera M, et al. 2012. MicroRNA-22 is induced by vitamin D and contributes to its antiproliferative, antimigratory and gene regulatory effects in colon cancer cells. *Hum. Mol. Genet.* 10:2157–65
9. Ambros V, Lee RC, Lavanway A, Williams PT, Jewell D. 2003. MicroRNAs and other tiny endogenous RNAs in *C. elegans*. *Curr. Biol.* 13:807–18
10. Arola-Arnal A, Blade C. 2011. Proanthocyanidins modulate microRNA expression in human HepG2 cells. *PLoS ONE* 6:e25982
11. Baer C, Claus R, Plass C. 2013. Genome-wide epigenetic regulation of miRNAs in cancer. *Cancer Res.* 73:473–77
12. Banerjee N, Talcott S, Safe S, Mertens-Talcott SU. 2012. Cytotoxicity of pomegranate polyphenolics in breast cancer cells in vitro and vivo: potential role of miRNA-27a and miRNA-155 in cell survival and inflammation. *Breast Cancer Res. Treat.* 136:21–34
13. Baselga-Escudero L, Blade C, Ribas-Latre A, Casanova E, Salvado MJ, et al. 2012. Grape seed proanthocyanidins repress the hepatic lipid regulators miR-33 and miR-122 in rats. *Mol. Nutr. Food Res.* 56:1636–46
14. Beveridge NJ, Tooney PA, Carroll AP, Tran N, Cairns MJ. 2009. Down-regulation of miR-17 family expression in response to retinoic acid induced neuronal differentiation. *Cell. Signal.* 21:1837–45
15. Boesch-Saadatmandi C, Wagner AE, Wolffram S, Rimbach G. 2012. Effect of quercetin on inflammatory gene expression in mice liver in vivo—role of redox factor 1, miRNA-122 and miRNA-125b. *Pharmacol. Res.* 65:523–30

15a. Boesch-Saadatmandi C, Loboda A, Wagner AE, Stachurska A, Jozkowicz A, et al. 2011. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: role of miR-155. *J. Nutr. Biochem.* 22:293–99

16. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, et al. 2004. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. USA* 101:2999–3004
17. Carrer M, Liu N, Grueter CE, Williams AH, Frisard MI, et al. 2012. Control of mitochondrial metabolism and systemic energy homeostasis by microRNAs 378 and 378*. *Proc. Natl. Acad. Sci. USA* 109:15330–35
18. Chakrabarti M, Ai W, Banik NL, Ray SK. 2013. Overexpression of miR-7-1 increases efficacy of green tea polyphenols for induction of apoptosis in human malignant neuroblastoma SH-SY5Y and SK-N-DZ cells. *Neurochem. Res.* 38:420–32
19. Chen QH, Wang QB, Zhang B. 2014. Ethnicity modifies the association between functional microRNA polymorphisms and breast cancer risk: a HuGE meta-analysis. *Tumour Biol.* 39:529–43
20. Chen Y, Liu W, Sun T, Huang Y, Wang Y, et al. 2013. 1,25-Dihydroxyvitamin D promotes negative feedback regulation of TLR signaling via targeting microRNA-155-SOCS1 in macrophages. *J. Immunol.* 190:3687–95
21. Chen Y, Zaman MS, Deng G, Majid S, Saini S, et al. 2010. MicroRNAs 221/222 and genistein-mediated regulation of ARHI tumor suppressor gene in prostate cancer. *Cancer Prev. Res.* 4:76–86
22. Chiyomaru T, Yamamura S, Fukhara S, Hidaka H, Majid S, et al. 2013. Genistein up-regulates tumor suppressor microRNA-574-3p in prostate cancer. *PLoS ONE* 8:e58929
23. Chiyomaru T, Yamamura S, Zaman MS, Majid S, Deng G, et al. 2012. Genistein suppresses prostate cancer growth through inhibition of oncogenic microRNA-151. *PLoS ONE* 7:e43812
24. Cortez MA, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. 2011. MicroRNAs in body fluids—the mix of hormones and biomarkers. *Nat. Rev. Clin. Oncol.* 8:467–77
25. Creemers EE, Tijsen AJ, Pinto YM. 2012. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? *Circ. Res.* 110:483–95
26. Davidson LA, Wang N, Sahah MS, Lupton JR, Ivanov I, Chapkin RS. 2009. *n*-3 Polyunsaturated fatty acids modulate carcinogen-directed non-coding microRNA signatures in rat colon. *Carcinogenesis* 30:2077–84
27. Derry MM, Raina K, Balaiya V, Jain AK, Shrotriya S, et al. 2013. Grape seed extract efficacy against azoxymethane-induced colon tumorigenesis in A/J mice: interlinking miRNA with cytokine signaling and inflammation. *Cancer Prev. Res.* 6:625–33

28. Di Leva G, Croce CM. 2013. miRNA profiling of cancer. *Curr. Opin. Genet. Dev.* 23:3–11
29. Elman J, Lindow M, Schutz S, Lawrence M, Petri A, et al. 2008. LNA-mediated microRNA silencing in non-human primates. *Nature* 452:896–99
30. Enquobahrie DA, Williams MA, Qiu C, Siscovick DS, Sorensen TK. 2011. Global maternal early pregnancy peripheral blood mRNA and miRNA expression profiles according to plasma 25-hydroxyvitamin D concentrations. *J. Matern. Fetal Neonatal Med.* 24:1002–12
31. Esau C, Davis S, Murray SF, Yu XX, Pandey SK, et al. 2006. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. *Cell Metab.* 3:87–98
32. Esau C, Kang X, Peralta E, Hanson E, Marcusson EG, et al. 2004. MicroRNA-143 regulates adipocyte differentiation. *J. Biol. Chem.* 279:52361–65
33. Fabbri M, Paone A, Calore F, Galli R, Gaudio E, et al. 2012. MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. *Proc. Natl. Acad. Sci. USA* 109:E2110–16
34. Filipowicz W, Bhattacharyya SN, Sonenberg N. 2008. Mechanisms of post-transcriptional regulation by microRNAs: Are the answers in sight? *Nat. Rev. Genet.* 9:102–14
35. Frost RJA, Oson EN. 2011. Control of glucose homeostasis and insulin sensitivity by the Let-7 family of microRNAs. *Proc. Natl. Acad. Sci. USA* 108:21075–80
36. Fullston T, Ohlsson Teague EM, Palmer NO, Deblasio MJ, Mitchell M, et al. 2013. Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. *FASEB J.* 27:4226–43
37. Gaedicke S, Zhang X, Schmelzer C, Lou Y, Doering F, et al. 2008. Vitamin E dependent microRNA regulation in rat liver. *FEBS Lett.* 582:3542–46
38. Gao SM, Yang JJ, Chen CQ, Chen JJ, Ye LP, et al. 2012. Pure curcumin decreases the expression of WT1 by upregulation of miR-15a and miR-16-1 in leukemic cells. *J. Exp. Clin. Cancer Res.* 31:27–36
39. Garzon R, Pichiorri F, Palumbo T, Visentini M, Aqeilan R, et al. 2007. MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. *Oncogene* 26:4148–57
40. Giangreco AA, Vaishnav A, Wagner D, Finelli A, Fleshner N, et al. 2013. Tumor suppressor microRNAs, miR-100 and -125b, are regulated by 1,25-dihydroxyvitamin D in primary prostate cells and in patient tissue. *Cancer Prev. Res.* 6:483–94
41. Gocek E, Wang X, Liu X, Liu CG, Studzinski GP. 2011. MicroRNA-32 upregulation by 1,25-dihydroxyvitamin D_3 in human myeloid leukemia cells leads to Bim targeting and inhibition of AraC-induced apoptosis. *Cancer Res.* 71:6230–39
42. Gommans WM, Berezikov E. 2012. Controlling miRNA regulation in disease. *Methods Mol. Biol.* 822:1–18
43. Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. 2006. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Res.* 34:D140–44
44. Gu S, Chan WY. 2012. Flexible and versatile as a chameleon—sophisticated functions of microRNA-199a. *Int. J. Mol. Sci.* 13:8449–66
45. Guan H, Liu C, Chen Z, Wang L, Li C, et al. 2013. 1,25-Dihydroxyvitamin D_3 up-regulates expression of hsa-let-7a-2 through the interaction of VDR/VDRE in human lung cancer A549 cells. *Gene* 522:142–46
46. Hagiwara K, Kosaka N, Yoshioka Y, Takahashi R-u, Takeshita F, Ochiya T. 2012. Stilbene derivatives promote Ago2-dependent tumour-suppressive microRNA activity. *Sci. Rep.* 2:314
47. Han Z, Yang Q, Liu B, Wu J, Li Y, et al. 2012. MicroRNA-622 functions as a tumor suppressor by targeting K-Ras and enhancing the anticarcinogenic effect of resveratrol. *Carcinogenesis* 33:131–39
48. Hassan ZK, Al-Olayan EM. 2012. Curcumin reorganizes miRNA expression in a mouse model of liver fibrosis. *Asian Pac. J. Cancer Prev.* 13:5405–8
49. Hirata H, Ueno K, Nakajima K, Tabatabai ZL, Hinoda Y, et al. 2013. Genistein downregulates onco-miR-1260b and inhibits Wnt-signalling in renal cancer cells. *Br. J. Cancer* 108:2070–78
50. Hoekstra M, Van der Sluis RJ, Kuiper J, Van Berkel TJ. 2012. Nonalcoholic fatty liver disease is associated with an altered hepatocyte microRNA profile in LDL receptor knockout mice. *J. Nutr. Biochem.* 23:622–28
51. Iorio MV, Croce CM. 2012. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. *EMBO Mol. Med.* 4:143–59

52. Izzotti A, Larghero P, Cartiglia C, Longobardi M, Pfeffer U, et al. 2010. Modulation of microRNA expression by budesonide, phenyl isothiocyanate and cigarette smoke in mouse liver and lung. *Carcinogenesis* 31:894–901
53. Jeon T, Park JW, Ahn J, Jung CH, Ha TY. 2013. Fisetin protects against hepatosteatosis in mice by inhibiting miR-378. *Mol. Nutr. Food Res.* 57:1931–37
54. Ji X, Wang Z, Geamanu A, Goja A, Sarkar FH, Gupta SV. 2012. Delta-tocotrienol suppresses Notch-1 pathway by upregulating miR-34a in nonsmall cell lung cancer cells. *Int. J. Cancer* 131:2668–77
55. Jian P, Li ZW, Fang TY, Jian W, Zhuan Z, et al. 2011. Retinoic acid induces HL-60 cell differentiation via the upregulation of miR-663. *J. Hemat. Oncol.* 4:20–28
56. Jin Y. 2011. 3,3′-Diindolylmethane inhibits breast cancer cell growth via miR-21-mediated Cdc25a degradation. *Mol. Cell. Biochem.* 358:345–54
57. Jordan SD, Kruger M, Willmes DM, Redemann N, Wunderlich FT, et al. 2011. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. *Nat. Cell Biol.* 13:434–46
58. Jorde R, Svartberg J, Joakimsen RM, Coucheron DH. 2012. Plasma profile of microRNA after supplementation with high doses of vitamin D3 for 12 months. *BMC Res. Notes* 5:245
59. Joven J, Espinel E, Rull A, Aragones G, Rodriguez-Gallego E, et al. 2012. Plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice. *Biochim. Biophys. Acta* 1820:894–99
60. Kasiappan R, Shen Z, Tse AKW, Jinwal U, Tang J, et al. 2012. 1,25-Dihydroxyvitamin D_3 suppresses telomerase expression and human cancer growth through microRNA-498. *J. Biol. Chem.* 287:41297–309
61. Kosaka N, Izumi H, Sekine K, Ochiya T. 2010. microRNA as a new immune-regulatory agent in breast milk. *Silence* 1:7
62. Kutay H, Bai S, Datta J, Motiwala T, Pogribny I, et al. 2006. Downregulation of miR-122 in the rodent and human hepatocellular carcinomas. *J. Cell. Biochem.* 99:671–78
63. Lam TK, Shao S, Zhao Y, Marincola F, Pesatori A, et al. 2012. Influence of quercetin-rich food intake on microRNA expression in lung cancer tissues. *Cancer Epidemiol. Biomarkers Prev.* 21:2176–84
64. Li H, Xia N, Forstermann U. 2012. Cardiovascular effects and molecular targets of resveratrol. *Nitric Oxide* 26:102–10
65. Li Y, Kong D, Ahmad A, Bao B, Dyson G, Sarkar FH. 2012. Epigenetic deregulation of miR-29a and miR-1256 by isoflavone contributes to the inhibition of prostate cancer cell growth and invasion. *Epigenetics* 7:940–49
66. Li Y, VandenBoom TG, Kong D, Wang Z, Ali S, et al. 2009. Up-regulation of miR-200 and let-7 by natural agents leads to the reversal of epithelial-to-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Cancer Res.* 69:6704–12
67. Li Y, VandenBoom TG, Wang Z, Kong D, Ali S, et al. 2010. miR-146a suppresses invasion of pancreatic cancer cells. *Cancer Res.* 70:1486–95
68. Liang Y, Li Y, Li Z, Liu Z, Zhang Z, et al. 2012. Mechanism of folate deficiency-induced apoptosis in mouse embryonic stem cells: cell cycle arrest/apoptosis in G1/G0 mediated by microRNA-302a and tumor suppressor gene *Lats2*. *Int. J. Biochem. Cell Biol.* 44:1750–60
69. Lisse TS, Chun RF, Rieger S, Adams JS, Hewlson M. 2013. Vitamin D activation of functionally distinct regulatory miRNAs in primary human osteoblasts. *J. Bone Miner. Res.* 28:1478–88
70. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, et al. 2005. MicroRNA expression profiles classify human cancers. *Nature* 435:834–38
71. Ma X, Ma C, Zheng X. 2013. MicroRNA-155 in the pathogenesis of atherosclerosis: a conflicting role? *Heart Lung Circ.* 22:811–18
72. Madrigal-Matute J, Rotlan N, Aranda JF, Fernandez-Hernando C. 2013. MicroRNAs and atherosclerosis. *Curr. Atheroscler. Rep.* 15:322–30
73. Majid S, Dar AA, Saini S, Chen Y, Shahryari V, et al. 2010. Regulation of minichromosome maintenance gene family by microRNA-1296 and genistein in prostate cancer. *Cancer Res.* 70:2809–18
74. Mandal CC, Ghosh-Choudhury T, Dey N, Choudhury GG, Ghosh-Choudhury N. 2012. miR-21 is targeted by omega-3 polyunsaturated fatty acid to regulate breast tumor CSF-1 expression. *Carcinogenesis* 33:1897–908

75. Marsit CJ, Eddy K, Kelsey KT. 2006. MicroRNA responses to cellular stress. *Cancer Res.* 22:10843–48
76. Mathieu J, Ruohola-Baker H. 2013. Regulation of stem cell populations by microRNAs. *Adv. Exp. Med. Biol.* 786:329–51
77. McCann SE, Liu S, Wang D, Shen J, Hu Q, et al. 2013. Reduction of dietary glycaemic load modifies the expression of microRNA potentially associated with energy balance and cancer pathways in premenopausal women. *Br. J. Nutr.* 109:5850592
78. Melkamu T, Zhang X, Tan J, Zeng Y, Kassie F. 2010. Alteration of microRNA expression in vinyl carbamate-induced mouse lung tumors and modulation by the chemopreventive agent indole-3-carbinol. *Carcinogenesis* 31:252–58
79. Meseguer S, Mudduluru G, Escamilla JM, Allgayer H, Barettino D. 2011. MicroRNAs-10a and -10b contribute to retinoic acid-induced differentiation of neuroblastoma cells and target the alternative splicing regulatory factor SFRS1 (SF2/ASF). *J. Biol. Chem.* 286:4150–64
80. Milagro FI, Miranda J, Portillo MP, Fernandez-Quintela A, Campion J, Martinez JA. 2013. High-throughput sequencing of microRNAs in peripheral blood mononuclear cells: identification of potential weight loss biomarkers. *PLoS ONE* 8:e54319
81. miRBase: the microRNA database. 2013. Release 20. **http://www.mirbase.org**
82. Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, et al. 2011. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. *Biosci. Rep.* 31:185–97
83. Mukhopadhyay P, Das S, Ahsan MK, Otani H, Das DK. 2012. Modulation of microRNA 20b with resveratrol and longevinex is linked with their potent and anti-angiogenic action in the ischaemic myocardium and synergistic effects of resveratrol and γ-tocotrienol. *J. Cell Mol. Med.* 16:2504–17
84. Mukhopadhyay P, Mukherjee S, Ahsan K, Bagchi A, Pascher P, Das DK. 2010. Restoration of altered microRNA expression in the ischemic heart with resveratrol. *PLoS ONE* 5:e15705
85. Mukhopadhayay P, Pacher P, Das DK. 2011. MicroRNA signatures of resveratrol in the ischemic heart. *Ann. N. Y. Acad. Sci.* 1215:109–16
86. Murase T, Misawa K, Minegisi Y, Aoki M, Ominami H, et al. 2010. Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice. *Am. J. Physiol.* 300:E122–33
87. Nair VS, Maeda LS, Ioannidis JP. 2012. Clinical outcome prediction by microRNAs in human cancer: a systematic review. *J. Natl. Cancer Inst.* 104:528–40
88. Nana-Sinkam SP, Croce CM. 2013. Clinical applications for microRNAs in cancer. *Clin. Pharmacol. Ther.* 93:98–104
89. Noratto GD, Angel-Morales G, Talcott ST, Mertens-Talcott SU. 2011. Polyphenolics from acai (*Euterpe Oleracea* Mart.) and red muscadine grape (*Vitis rotundifolia*) protect human umbilical vascular endothelial cells (HUVEC) from glucose- and lipopolysaccharide (LPS)-induced inflammation and target microRNA-126. *J. Agric. Food Chem.* 59:7999–8012
90. Noratto GD, Jutooru I, Safe S, Ngel-Morales G, Mertens-Talcott SU. 2013. The drug resistance suppression induced by curcuminoids in colon cancer SW-480 cells is mediated by reactive oxygen species-induced disruption of the microRNA-27a-ZBTB10-Sp axis. *Mol. Nutr. Food Res.* 57:1638–48
91. Noratto GD, Kim Y, Talcott ST, Mertens-Talcott SU. 2011. Flavonol-rich fractions of yaupon holly leaves (*Ilex vomitoria*, Aquifoliaceae) induce microRNA-146a and have anti-inflammatory and chemopreventive effects in intestinal myofibroblast CCD-18Co cells. *Fitoterapia* 82:557–69
92. Ortega FJ, Mercader JM, Catalán V, Moreno-Navarrete JM, Pueyo N, et al. 2013. Targeting the circulating microRNA signature of obesity. *Clin. Chem.* 59:781–92
93. Padi SKR, Zhang Q, Rustum YM, Morrison C, Guo B. 2013. MicroRNA-627 mediates the epigenetic mechanisms of vitamin D to suppress proliferation of human colorectal cancer cells and growth of xenograft tumors in mice. *Gastroenterology* 145:437–46
94. Parasramka MA, Dashwood WM, Wang R, Abdelli A, Bailey GS, et al. 2012. MicroRNA profiling of carcinogen-induced rat colon tumors and the influence of dietary spinach. *Mol. Nutr. Food Res.* 56:1259–69
95. Park JH, Ahn J, Kim S, Kwon DY, Ha TY. 2011. Murine hepatic miRNAs expression and regulation of gene expression in diet-induced obese mice. *Mol. Cells* 31:33–38

96. Parra P, Serra F, Palou A. 2010. Expression of adipose microRNAs is sensitive to dietary conjugated linoleic acid treatment in mice. *PLoS ONE* 5:e13005
97. Peng X, Vaishnav A, Murillo G, Alimirah F, Torres KEO, Mehta RG. 2010. Protection against cellular stress by 25-hydroxyvitamin D_3 in breast epithelial cells. *J. Cell Biochem.* 110:1324–33
98. Perron MP, Provost P. 2009. Protein components of the microRNA pathway and human diseases. *Methods Mol. Biol.* 487:369–85
99. Poy MN, Hausser J, Trajovski M, Braun M, Collins S, et al. 2009. miR-375 maintains normal pancreatic alpha- and beta-cell mass. *Proc. Natl. Acad. Sci. USA* 106:5813–18
100. Prats-Puig A, Ortega FJ, Mercader JM, Moreno-Navarrete JM, Moreno M, et al. 2013. Changes in circulating microRNAs are associated with childhood obesity. *J. Clin. Endocrinol. Metab.* 98:E1655–60
101. Roy S, Levi E, Majumdar APN, Sarkar FH. 2012. Expression of miR-34 is lost in colon cancer which can be re-expressed by a novel agent CDF. *J. Hematol. Oncol.* 5:58–64
102. Ryan BM, Robles AI, Harris CC. 2010. Genetic variation in microRNA networks: the implications for cancer research. *Nat. Rev. Cancer* 10:389–402
103. Ryu MS, Langkamp-Henken B, Chang SM, Shankar MN, Cousins RJ. 2011. Genomic analysis, cytokine expression, and microRNA profiling reveal biomarkers of human dietary zinc depletion and homeostasis. *Proc. Natl. Acad. Sci. USA* 108:20970–75
104. Saini S, Arora S, Majid S, Shahryari V, Chen Y, et al. 2011. Curcumin modulates microRNA-203-mediated regulation of the Src-Akt axis in bladder cancer. *Cancer Prev. Res.* 4:1698–709
105. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. 2011. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* 146:353–58
106. Sarveswaran S, Liroff J, Zhou Z, Nikitin AY, Ghosh J. 2010. Selenite triggers rapid transcriptional activation of p53, and p53-mediated apoptosis in prostate cancer cells: implication for the treatment of early-stage prostate cancer. *Int. J. Oncol.* 36:1419–28
107. Sayed D, Abdellatif M. 2011. MicroRNAs in development and disease. *Physiol. Rev.* 91:827–87
108. Shah MS, Davidson LA, Chapkin RS. 2012. Mechanistic insights into the role of microRNAs in cancer: influence of nutrient crosstalk. *Front. Genet.* 3:305
109. Sheth S, Jajoo S, Kaur T, Mukherjea D, Sheehan K, et al. 2012. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/microRNA-21 pathway. *PLoS ONE* 7:e51655
110. Siaj R, Sauer V, Stöppeler S, Gerβ J, Spiegel HU, et al. 2012. Longitudinal analysis of serum miR-122 in a rat model of Wilson's disease. *Hepatol. Int.* 6:770–77
111. Siddiqui IA, Asim M, Hafeez BB, Adhami VM, Tarapore RS, Mukhtar H. 2011. Green tea polyphenol EGCG blunts androgen receptor function in prostate cancer. *FASEB J.* 25:1198–207
112. Singh B, Ronghe AM, Chatterjee A, Bhat NK, Bhat HK. 2013. microRNA-93 regulates NRF2 expression and is associated with breast carcinogenesis. *Carcinogenesis* 34:1165–72
113. Snow JW, Hale AE, Isaacs SK, Baggish AL, Chan SY. 2013. Ineffective delivery of diet-derived microRNAs to recipient animal organisms. *RNA Biol.* 10:1107–16
114. Soubani O, Ali AS, Logna F, Ali S, Philip PA, Sarkar FH. 2012. Re-expression of *miR-200* by novel approaches regulates the expression of PTEN and MT1-MMP in pancreatic cancer. *Carcinogenesis* 8:1563–71
115. Starega-Roslan J, Koscianska E, Kozlowski P, Krzyzosiak WJ. 2011. The role of the precursor structure in the biogenesis of microRNA. *Cell Mol. Life Sci.* 68:2859–71
116. Stefani G, Slack F. 2006. MicroRNAs in search of a target. *Cold Spring Harb. Symp. Quant. Biol.* 71:129–34
117. Subramaniam D, Ponnurangam S, Ramamoorthy P, Standing D, Battafarano RJ, et al. 2012. Curcumin induces cell death in esophageal cancer cells through modulating Notch signaling. *PLoS ONE* 7:e30590
118. Sun Q, Cong R, Yan H, Gu H, Zeng Y, et al. 2009. Genistein inhibits growth of human uveal melanoma cells and affects microRNA-27a and target gene expression. *Oncol. Rep.* 22:563–67
119. Takanabe R, Ono K, Abe Y, Takaya T, Horie T, et al. 2008. Up-regulated expression of microRNA-143 in association with obesity in adipose tissue of mice fed high fat diet. *Biochem. Biophys. Res. Commun.* 376:728–32
120. Tarver JE, Sperling EA, Nailor A, Heimberg AM, Robinson JM, et al. 2013. miRNAs: small genes with big potential in metazoan phylogenetics. *Mol. Biol. Evol.* 30:2369–82

121. Terao M, Fratelli M, Kurosaki M, Zanetti A, Guarnaccia V, et al. 2011. Induction of miR-21 by retinoic acid in estrogen receptor-positive breast carcinoma cells. *J. Biol. Chem.* 286:4027–42
122. Thornton JE, Gregory RI. 2012. How does Lin28 let-7 control development and disease? *Trends Cell Biol.* 22:474–82
123. Tili EI, Michaille JJ, Adair B, Alder H, Limagne E, et al. 2010. Resveratrol decreases the levels of miR155 by upregulating miR-663, a microRNA targeting JunB and JunD. *Carginogenesis* 31:1561–66
124. Ting HJ, Messing J, Yasmin-Karim S, Lee YF. 2013. Identification of microRNA-98 as a therapeutic target inhibiting prostate cancer growth and a biomarker induced by vitamin D. *J. Biol. Chem.* 288:1–9
125. Tomé-Carneiro J, Larrosa M, Yáñez-Gascón MJ, Dávalos A, Gil-Zamorano J, et al. 2013. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. *Pharmacol. Res.* 72:69–82
126. Trajovski M, Hausser J, Soutschek J, Bhat B, Akin A, et al. 2012. microRNAs 103 and 107 regulate insulin sensitivity. *Nature* 474:649–54
127. Tryndyak VP, Latendresse JR, Montgomery B, Ross SA, Beland FA, et al. 2012. Plasma microRNAs are sensitive indicators of inter-strain differences in the severity of liver injury induced in mice by a choline- and folate-deficient diet. *Toxicol. Appl. Pharmacol.* 262:52–59
128. Tryndyak VP, Ross SA, Beland FA, Pogribny IP. 2009. Down-regulation of the microRNAs miR-34a, miR-127 and miR-200b in rat liver during hepatocarcinogenesis induced by a methyl-deficient diet. *Mol. Carcinog.* 48:479–87
129. Tsang WP, Kwok TT. 2010. Epigallocatechin gallate up-regulation of miR-16 and induction of apoptosis in human cancer cells. *J. Nutr. Biochem.* 21:140–46
130. Turchinovich A, Weiz L, Burwinkel B. 2012. Extracellular miRNAs: the mystery of their origin and function. *Trends Biochem. Sci.* 37:460–65
131. Turchinovich A, Weiz L, Langheinz A, Burwinkel B. 2011. Characterization of extracellular circulating microRNA. *Nucleic Acids Res.* 39:7223–33
132. Tzur G, Israel A, Levy A, Benjamin H, Meiri E, et al. 2009. Comprehensive gene and microRNA expression profiling reveals a role for microRNAs in human liver development. *PLoS ONE* 4:e7511
133. Vella MC, Slack FJ. 2005. *C. elegans* microRNAs. In *WormBook*, ed. *C. elegans* Res. Community, pp. 1–9. doi/10.1895/wormbook.1.26.1. **http://www.wormbook.org**
134. Vinciguerra M, Sgroi A, Veyrat-Durebex C, Rubbia-Brandt L, Buhler LH, Foti M. 2009. Unsaturated fatty acids inhibit the expression of tumor suppressor phosphatase and tensin homolog (PTEN) via microRNA-21 up-regulation in hepatocytes. *Hepatology* 49:1176–84
135. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, et al. 2006. A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc. Natl. Acad. Sci. USA* 103:2257–61
136. Wagner AE, Boesch-Saadatmandi C, Dose J, Schultheiss G, Rimbach G. 2012. Anti-inflammatory potential of allyl-isothiocyanate—role of Nrf2, NF-κB and microRNA-155. *J. Cell Mol. Med.* 16:836–43
137. Wang D, Xia M, Yan X, Li D, Wang L, et al. 2012. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. *Circ. Res.* 111:967–81
138. Wang H, Bian S, Yang CS. 2011. Green tea polyphenol EGCG suppresses lung cancer growth through upregulating miR-210 expression caused by stabilizing HIF-1α. *Carcinogenesis* 32:1881–89
139. Wang K, Li H, Yuan Y, Etheridge A, Zhou Y, et al. 2012. The complex exogenous RNA spectra in human plasma: an interface with human gut biota? *PLoS ONE* 7:e51009
140. Wang WL, Welsh J, Tenniswood M. 2013. 1,25-Dihydroxyvitamin D_3 modulates lipid metabolism in prostate cancer cells through miRNA mediated regulation of PPARA. *J. Steroid Biochem. Mol. Biol.* 136:247–51
141. Wang X, Gocek E, Liu CG, Studzinski GP. 2009. microRNAs181 regulate the expression of p27 in human myeloid leukemia cells induced to differentiate by 1,25-dihydroxyvitamin D_3. *Cell Cycle* 8:736–41
142. Wang Y, Hu X, Greshock J, Shen L, Yang X, et al. 2012. Genomic DNA copy-number alterations of the let-7 family in human cancers. *PLoS ONE* 7:e44399
143. Wei Y, Nazari-Jahantigh M, Neth P, Weber C, Schober A. 2013. MicroRNA-126, -145, and -155: a therapeutic triad in atherosclerosis? *Arterioscler. Thromb. Vasc. Biol.* 33:449–54

144. Wen XY, Wu SY, Li ZQ, Liu ZQ, Zhang JJ, et al. 2009. Ellagitannin (BJA3121), an anti-proliferative natural polyphenol compound, can regulate the expression of miRNAs in $HepG_2$ cancer cells. *Phytother. Res.* 23:778–84
145. Witwer KW, McAlexander MA, Queen SE, Adams RJ. 2013. Real-time quantitative PCR and droplet digital PCR for plant miRNAs in mammalian blood provide little evidence for general uptake of dietary miRNAs: limited evidence for general uptake of dietary plant xenomiRs. *RNA Biol.* 10:1080–86
146. Wu N, Wu C, Hu R, Li M, Feng H. 2011. Ginsenoside Rh2 inhibits glioma cell proliferation by targeting microRNA-128. *Acta Pharmacol. Sin.* 32:345–53
147. Xia J, Duan Q, Ahmad A, Bao B, Banerjee S, et al. 2012. Genistein inhibits cell growth and induces apoptosis through up-regulation of miR-34a in pancreatic cancer cells. *Curr. Drug Targets* 13:1750–56
148. Xie H, Lim B, Lodish HF. 2009. MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity. *Diabetes* 58:1050–57
149. Yamada H, Suzuki K, Ichino N, Ando Y, Sawada A, et al. 2013. Associations between circulating microRNAs (miR-21, miR-34a, miR-122 and miR-451) and non-alcoholic fatty liver. *Clin. Chim. Acta* 424:99–103
150. Yang J, Cao Y, Sun J, Zhang Y. 2010. Curcumin reduces the expression of Bcl-2 by upregulating miR-15a and miR-16 in MCF-7 cells. *Med. Oncol.* 27:1114–18
151. Yang YM, Seo SY, Kim TH, Kim SG. 2012. Decrease of miR-122 causes hepatic insulin resistance by inducing protein tyrosine phosphatase 1B, which is reversed by licorice flavonoid. *Hepatology* 56:2209–20
152. Zaman MS, Shahyrar V, Deng G, Thamminana S, Saini S, et al. 2012. Up-regulation of microRNA-21 correlates with lower kidney cancer survival. *PLoS ONE* 7:e31060
153. Zampetaki A, Kiechl S, Drozdov I, Willeit P, Mayr U, et al. 2010. Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. *Circ. Res.* 107:810–17
154. Zhang J, Du Y, Wu C, Ren X, Ti X, et al. 2010. Curcumin promotes apoptosis in human lung adenocarcinoma cells through miR-186* signaling pathway. *Oncol. Rep.* 24:1217–23
155. Zhang J, Zhang F, Didelot X, Bruce KD, Cagampang FR, et al. 2009. Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring. *BMC Genomics* 10:478
156. Zhang L, Hou D, Chen X, Li D, Zhu L, et al. 2012. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res.* 22:107–26
157. Zhang MW, Jin MJ, Yu YX, Zhang SC, Liu B, et al. 2012. Associations of lifestyle-related factors, hsa-miR-149 and hsa-miR-605 gene polymorphisms with gastrointestinal cancer risk. *Mol. Carcinog.* 51(Suppl. 1):E21–31
158. Zhao H, Guan J, Lee HM, Sui Y, He L, et al. 2010. Up-regulated pancreatic tissue microRNA-375 associates with human type 2 diabetes through beta-cell deficit and islet amyloid deposition. *Pancreas* 39:843–46
159. Zhao JJ, Sun DG, Wang J, Liu SR, Zhang CY, et al. 2008. Retinoic acid downregulates microRNAs to induce abnormal development of spinal cord in spina bifida rat model. *Child Nerv. Syst.* 24:485–92
160. Zhong H, Wang H, Yang S, Zhong J, Wang T, et al. 2010. Targeting Smad4 links microRNA-146a to the TGF-β pathway during retinoid acid induction in acute promyelocytic leukemia cell line. *Int. J. Hematol.* 92:129–35
161. Zhong Z, Dong Z, Yang L, Chen X, Gong Z. 2012. Inhibition of proliferation of human lung cancer cells by green tea catechins is mediated by upregulation of let-7. *Exp. Ther. Med.* 4:267–72
162. Zhu H, Dougherty U, Robinson V, Mustafi R, Pekow J, et al. 2011. EGFR signals downregulate tumor suppressors miR-143 and miR-145 in Western diet-promoted murine colon cancer: role of G1 regulators. *Mol. Cancer Res.* 9:960–75
163. Zhu H, Shyh-Chang N, Segre AV, Shinoda G, Shah SP, et al. 2011. The Lin28/let-7 axis regulates glucose metabolism. *Cell* 147:81–94