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XenomiRs and miRNA homeostasis in health and disease

Evidence that diet and dietary miRNAs directly and indirectly influence circulating miRNA profiles

Kenneth W. Witwer

Department of Molecular and Comparative Pathobiology; The Johns Hopkins University School of Medicine; Baltimore, MD USA

Contributions of dietary miRNAs to circulating small RNA profiles would have profound implications for interpretation of miRNA biomarker studies: presumptive disease-specific markers might instead indicate responses to disease-associated quantitative or qualitative dietary alteration. This examination weighs the evidence for a 2-fold hypothesis: first, that ingested biological matter contributes directly to the miRNA complement of body compartments; and second, that these diet-derived exogenous miRNAs (or "xenomiRs") affect total miRNA profiles as part of a circulating miRNA homeostasis that is altered in many diseases. Homeostasis of high-density lipoprotein (HDL), a known miRNA carrier—provides a model as a proposed component of broader miRNA homeostasis. Further research into the dietary xenomiR hypothesis is needed to ensure rigor in the search for truly disease-specific miRNA biomarkers.

Keywords: biomarker, microRNA, HDL, LDL, cholesterol, diet, homeostasis, xenomiR, nutrition, cancer

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; HIV, human immunodeficiency virus; HCV, hepatitis C virus; siRNA, small interfering RNA; xenomiR, exogenous miRNA

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Correspondence to: Kenneth W. Witwer; Email:kwitwer1@jhmi.edu

Introduction

Interest in microRNAs has expanded rapidly during the past decade as these short, single-stranded RNA oligonucleotides, once considered a curiosity of the model organism *C. elegans*, have been identified as managers of mRNA stability and translation,[1,2] and as biomarkers of disease.[3,4] Presence in non-invasively obtained body fluids renders miRNAs particularly attractive as biomarkers, while the types and provenance of vehicles that protect circulating miRNAs from degradation may provide insight into disease processes. These vehicles include exosomes and microvesicles,[5] lipid-protein complexes such as high-density lipoproteins (HDL),[6] and protein complexes[7,8] similar or identical to those that contain miRNA inside the cell.[9] miRNA biomarker studies in oncology have greatly outnumbered investigations of small RNA in all other diseases combined[10]—and for good reason, since the largely clonal nature of many cancers simplifies detection of altered profiles in this high-priority group of diseases—but miRNA associations have also been reported in other conditions, from brain and metabolic disorders to infectious diseases.[11]

It may be premature, however, to conclude from existing biomarker studies that disease-associated miRNA profile changes are necessarily and in their entirety attributable directly to disease. Differential expression of miRNAs could instead be due to unrelated or indirect factors (**Table 1**), but analyses of potential confounders are not usually included in biomarker studies. Perhaps the largest pachyderm in the disease biomarker room, though, is diet, which may exert 3-fold modulation on circulating miRNA profiles:

(1) The indirect influence of dietary substances on endogenous miRNA production;

(2) The direct entry into the circulating miRNA population of dietary exogenous miRNAs, or "xenomiRs," many of which would be largely or wholly indistinguishable, sequence- and function-wise, from endogenous miRNAs; and

(3) The indirect influence of dietary xenomiRs and their vehicles on known

Table 1. Potentially confounding factors in miRNA disease biomarker studies

Factors influencing miRNA profiles	Selected example(s)
Physical activity	miRNA profiles in rat[12,13] and in human muscle,[14] circulating immune cells,[15] and extracellular blood fractions[16]
Age disparity	Brain profiles in macaques and humans[17]
Ethnicity	miRNA profiles of cells derived from European-Americans and Nigerians[18]
Immune activation	Endotoxemia,[19] acute SIV infection[20]
Pharmacologic substances	Circulating miR-134 during lithium and valproic acid treatment of bipolar disorder[21]
Drugs of abuse	Cocaine,[22] heroin[23] and alcohol[24-26]
Cell populations	Differing proportions of circulating blood cell types influence circulating miRNA profiles[27]
Technical artifact	Batch effects from separate processing of disease and control samples;[97-99] extent of hemolysis[100]

and unknown homeostatic mechanisms that maintain the concentration of circulating miRNA-containing vehicles (lipoprotein particles, exosomes, microvesicles, and specific protein complexes) and could thus effect changes in the concentration of specific miRNAs in response to diet.

The first influence of diet is well established. From vitamin A to zinc, nutrients affect miRNA production in animals[28-30] and plants.[31] This examination will not review these studies but will instead focus on aspects of diet that distinguish it from other potential confounders of disease biomarker studies: food itself contains miRNAs that, if absorbed, would contribute directly to apparent circulating miRNA "expression," and indirectly by affecting homeostasis of miRNA vehicles such as HDL. Because diet and disease are closely linked, these possibilities present wide-ranging implications for the investigation of miRNA disease biomarkers.

The diet-disease axis. The interrelatedness of disease and diet is evident, for example, in cancers, most cases of which are associated with one or more of the following related, often definitionally overlapping, conditions: anorexia, malnutrition, weight loss, cachexia, and wasting.[32-34] Each is usually connected with reduced alimentary intake, often in step with metabolic changes and negative energy balance.[35-37] Qualitative dietary changes may also accompany cancers, especially during advanced disease and physical blockages that necessitate enteral or parenteral nutrition with highly processed product that are less likely than fresh food to contain intact miRNAs. (Cooking reduces the amounts of measurable miRNA in vegetable foods by as much as 100-fold,[38] while mixing, storage, and drying reduce levels in milk products.[39])

Infectious diseases provide a second broad example of the diet-disease axis. Loss of appetite is part of the acute cytokine-induced "sickness behavior" accompanying innate immune responses.[40] Specific pathogens may also precipitate chronic nutrition-related conditions, e.g., wasting and other nutrition-related conditions that preceed or define AIDS.[41,42] While these conditions may stem from metabolic alterations, alimentary intake is usually changed as well, and appetite stimulants may be necessary for cachexic patients.[43] A recent study of nutrition and HCV-infected individuals concluded that "(m)alnutrition occurs early…and progresses relentlessly throughout the spectrum of HCV disease."[44] Finally, some infectious diseases disproportionately afflict individuals with particular socioeconomic backgrounds and attendant diets. Unless controls are carefully selected with attention to nutrition status, diet itself may distinguish patients from controls.

Dietary miRNA uptake and function in animals. Because miRNAs are found in animals and plants, and miRNA-like species are present in fungi,[45] almost all fresh foods contain small RNAs that could contribute to the circulating miRNA population. Even processed foods—e.g., cooked rice, potatoes, cabbage,[38] and baby milk formula[39]—contain miRNAs, albeit at reduced concentrations. That these miRNAs could be delivered to the blood is supported by oral delivery of pharmacological preparations of siRNA.[46-48] When protected from the acidic and enzymatic environment of the digestive tract by lipids, proteins, or polysaccharides, ingested small RNA molecules may enter into circulation through the gut. Protection is achieved by artificial shells for therapeutic siRNAs, but multiple protective means are available for food miRNAs, including natural lipid vesicles[49] and protein complexes.[38] This process is thought to involve transcytosis across the gut epithelium, particularly by M cells of the Peyer's patches. Macrophages and T-cells of the gut-associated lymphoid tissue (GALT) have been implicated in subsequent distribution of RNA-containing complexes throughout the body,[47] and these cells contribute to the miRNA-containing circulating vesicle population.[50,51] It is possible that there are additional, uncharacterized mechanisms for uptake from the GI tract of unprotected small RNAs. Although unshielded miRNAs are degraded much more rapidly in an acidic environment than are miRNAs in fresh food, even these exposed miRNAs may survive for several hours,[38] long enough for uptake via receptor-mediated endocytosis or, speculatively, by uncharacterized transporters. (Interestingly, the first miRNA receptor was recently described.[52])

Direct support for uptake of dietary xenomiRs was lacking, however, until a recent report that miRNAs from dietary plant matter circulate in the blood, enter multiple tissues, including the liver, and even regulate genes in mammals[38] with rice-based diets. The authors specifically reported that the LDL receptor associated protein LDLRAP1 contained a plant miRNA target site in its 3' untranslated region and could be regulated by dietary miRNAs. (In the future, further genetic analyses will be useful to identify additional plant miRNA target sites in animal transcripts.) Several reviews of these findings appeared in the popular and

Table 2. Plant miRNAs detected in human serum (adapted from Zhang, et al.[38])

miRNA	Detected in # of pools (out of 10)	# sequence reads/ sample (range)	# sequence reads/ sample (median)	% of total plant reads per sample	% of total miRNA reads per sample
miR160a	5	(3–42)	8		
miR162a	5	(1–18)	9		
miR171c	5	(2–131)	8		
miR169b	6	(1–1777)	89.5		
miR390a	6	(1–63)	7		
miR156 g	8	(3–87)	12		
miR157a	8	(27–6254)	356		
miR164a	9	(3–2126)	79		
miR172a	9	(1–1513)	294		
miR166a	10	(3–3397)	2905		
miR167a	10	(3–761)	483.5		
miR156a	10	(846–12363)	94.5	24–95	0.2–1.2
miR168a	10	(12–27758)	2852	0.5–54	0.001–2.8

scientific press,[53-55] often in the context of "cross-kingdom regulation" and speculated implications for herbal medicine and genetic engineering. It is important to emphasize that the data from this study do not suggest that all ingested miRNAs end up in the bloodstream in potentially functional quantities. While the investigators found 25 plant miRNAs by sequencing pools of human serum, only four were identified in all pools. Also, absolute numbers of specific miRNA sequence reads as well as relative proportions were quite variable (**Table 2**), even for the consistently detected miR156 and miR168a, which are among the most conserved plant miRNAs and the most abundant in nutritionally useful parts of plants and in pollen.[56] No low-abundance, species-specific miRNAs were reported. While it is thus unlikely that some of the speculative claims of Zhang, et al.'s reviewers are plausible—for example, that miRNAs specific to Chinese folk remedies contribute to their effects,[53] or that engineering of plants could expose humans to dangerous miRNAs[53]—the central conclusion of Zhang et al., stands: abundant dietary xenomiRs enter the mammalian bloodstream and have functional consequences in the liver.[38]

Despite the noted limitations, these findings raise important questions for biomarker research that have not yet been carefully reviewed, first and foremost the possibility that some proportion of miRNA biomarkers in disease studies may be xenomiRs of plant and animal origin. The authors showed that serum and liver plant miRNA concentrations were upregulated 2-fold or more following a dietary switch from processed to fresh food. This magnitude of regulation is consistent both with functional consequences, as underlined by the authors,[38,57,58] and with biomarker changes that have been reported in the literature.[59-61] If plant miRNAs—with plant-specific chemical modifications and surrounded by proteins foreign to the ingesting animal—can enter the bloodstream, it is probable that dietary animal miRNAs would follow a similar path. Indeed, artificial mammalian miR-150 was delivered to the blood by the oral route.[62] Albeit currently without experimental support, animal miRNAs could well undergo preferential uptake due to the "familiar" nature of their sequence and packaging. At the same time, sequence similarity greatly complicates analytical separation of xenomiRs from endogenous animal miRNAs. While the human genome does not contain sequences homologous to abundant plant miRNAs, abundant animal miRNAs are often 100% identical from fish to ruminants to humans. In existing biomarker reports, then, xenomiRs that are present have been conflated with endogenous miRNAs, the apparent concentration of which might thus differ based on diet quantity and quality. Experiments with carefully controlled diet or with food sources containing in vivo labeled miRNAs will be needed to identify these xenomiRs and their contributions to disease profiles.

When disease results in reduced food intake, as is often the case, we might exclusively expect a deficit of certain diet-derived miRNAs. Such a prediction might be overly simplistic, however, because it assumes that the direct effects of dietary miRNAs are the only effects or the predominant effects. However, miRNA profiling studies rarely identify uniform downmodulation of circulating miRNA concentrations, even with diseases such as cancers that can greatly affect food intake. This observation leads us to the next part of the dietary xenomiR hypothesis, proposing a mechanistically multipartite system of circulating miRNA homeostasis that is closely related to hunger impulses and metabolism.

Indirect effects of diet and xenomiRs on circulating miRNA homeostasis—the HDL example. A system of circulating miRNA homeostasis would include sensors to monitor miRNA concentration in the blood and mechanisms of miRNA release or uptake to replenish or deplete the extracellular pool of miRNAs. However, the lipids and proteins that protect extracellular miRNAs from degradation would also presumably preclude recognition by cell-surface receptors (note, though, the recent characterization of TLR8 as a miRNA sensor[52]). Plausibly, miRNA homeostasis would involve recognition of surface features of the various small vehicles that transport miRNAs. Maintenance

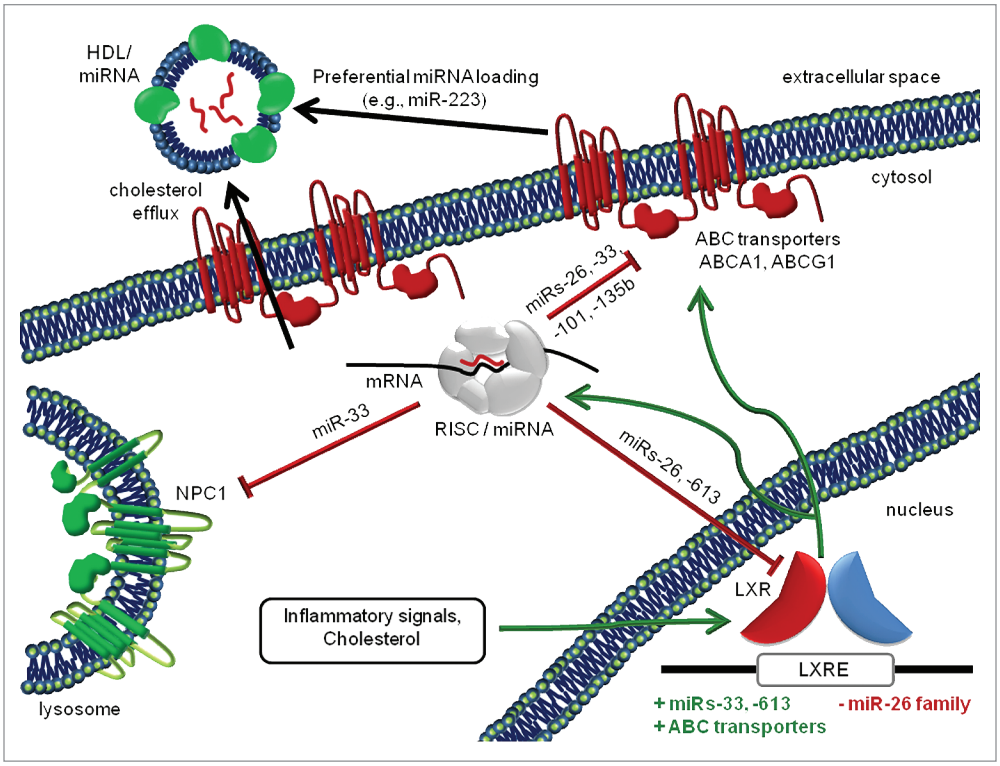

Figure 1. Cholesterol, HDL, and miRNAs. Mutual relationships of miRNAs and cholesterol transport components in the extracellular space, cytosol, lysosome, and nucleus (not to scale). Inhibitory and stimulatory effects are depicted in red and green, respectively. The mechanism(s) that impart specificity to miRNA HDL loading are unknown. Because of seemingly conflicting results concerning the effects of neutral sphyngomyelinase 2 on miRNA export,[6,63] nSMase2 is not depicted here.

of relatively constant levels of miRNA in circulation would then depend on homeostasis of miRNA vehicles. If inclusion of miRNA in these systems has evolutionary consequences and is not merely a bystander effect, each such system would likely involve:

- Feedback controls linking miRNAs and elements of vehicle-specific regulatory pathways
- Incorporation of specific miRNAs into specific vehicles
- A mechanism for sensing concentration of extracellular miRNA vehicles and release or uptake of the vehicles;
- Changes in appetite and/or metabolism that are direct or bystander effects of sensing.

Importantly, although not yet assembled into a whole from the standpoint of miRNA, it appears that each individual piece has already been characterized for at least one known extracellular miRNA vehicle: lipoprotein particles. We will now review this evidence, with a focus on HDL.

miRNAs regulate the machinery of cholesterol homeostasis. Recent advances have highlighted the role of miRNA in cholesterol homeostasis (**Fig. 1**). miR-33[64,65] and miR-26[66] family members, as well as miRs-106b,[67] -122,[68,69] -335,[70] -613,[71] and -758,[72] are reported to modulate governors of cholesterol efflux, uptake, synthesis, and HDL metabolism.[73] miRNA precursor transcription, in turn, is inhibited by cholesterol metabolism-related liver X receptors (LXRs).[66] Inhibition of miR-33 allows cholesterol efflux to increase, along with HDL particle concentrations, and miR-33 targets include members of additional metabolic pathways[74] (note, as well, further evidence of reciprocal influence of miRNA networks and metabolism.[75,76]) In a mouse model of atherosclerosis in which both copies of the LDL receptor gene are knocked out, miR-33 inhibition prompted increases in HDL levels, shrinkage of sclerotic plaques, and decreased inflammatory signaling.[77] Higher HDL and concomitantly reduced VLDL were also observed in primates.[78]

While miRNA-mediated modulation of cholesterol homeostasis would not strictly be required to establish HDL as a regulated carrier of miRNA, the existence of these mechanisms supports the hypothesis that miRNA homeostasis is an evolutionarily conserved corollary of HDL homeostasis.

Cholesterol-containing lipoprotein particles carry miRNA. The involvement of the ceramide pathway in miRNA export from cells[79] and the finding that some exported particles were cholesterol rich and exosome or sub-exosome-sized[63,80] prompted an investigation of lipoproteins as potential miRNA carriers.[6] In this study by the Remaley group, HDL particles were confirmed as miRNA vehicles, and they were found to harbor a unique miRNA profile: specific miRNAs, for example miR-223, were enriched in HDL RNA in comparison with RNA from the cells of origin (see **Fig. 1**).[6] Moreover, RNA-free reconstituted HDL particles were capable of miRNA incorporation.[6,81] miRNAs were also discovered in low-density

lipoproteins, although the miRNA profile of LDL more closely resembled that of exosomes.[6]

Based upon these studies, it is entirely possible that diet- or disease-related changes in HDL contents or concentration could affect overall circulating miRNA profiles sufficiently to confound biomarker studies. When recombinant HDL were recovered from the blood of mice that received high-fat or regular diets, concentrations of specific miRNAs—including commonly disease-associated miRNAs such as miRs-16, -92, -223, and members of the miR-27, -29, and -30 families—differed by as much as 64-fold or more (**Fig. S1**), while the human genetic disease hypercholesterolemia was associated with miRNA fold changes in the hundreds to thousands range.[6] It is not uncommon for proposed circulating miRNA biomarkers of cancer (for example, esophageal squamous cell carcinoma) to be differentially regulated by 3-fold or less in cancer patients vs. controls, or in before-and-after assessments of resection or chemotherapy.[59-61] Thus, although further studies are needed to analyze rigorously and in parallel HDL/LDL concentrations, the miRNA content of these lipoproteins, and overall circulating miRNA concentrations in health and specific diseases, there is ample reason to suspect that some proposed miRNA biomarkers could be significantly affected by HDL miRNAs.

Cellular receptors govern sensing, uptake, and release of miRNA-containing HDL. Circulating HDL particles—and their cargo of enriched miRNAs—are sensed and taken up by liver cells via scavenger receptor SCARB1. Although most abundant in liver, SCARB1 is expressed in other tissues,[82,83] suggesting that uptake of HDL miRNA throughout the body involves the HDL-SCARB1 interaction. It also appears that SCARB1 regulates release of HDL. SCARB1 initiates intracellular signaling[84] through a scaffold protein, PDZK1.[85] Both SCARB1 and PDZK1 knockout mice display increased cholesterol efflux and production of abnormal HDL particles,[86,87] along with altered endocrine, GI, and cardiac physiology,[85] supporting involvement of this pathway in both uptake and release of HDL miRNA. Interestingly, cholesterol conjugation has been used to deliver therapeutic miRNAs successfully in a mouse model of hepatocellular carcinoma.[88]

Changes in appetite and/or metabolism are associated with HDL sensing. If homeostases of miRNA and circulating particles are linked and dietary xenomiRs contribute to the extracellular miRNA pool, influence of miRNA vehicle concentration on nutrition intake (i.e., through appetite) would be expected. In cholesterol homeostasis, there is already ample evidence for this. In health, appetite is governed largely by hypothalamic responses to leptin and other hormones, in turn influenced by energy balance and tied to insulin signaling and cholesterol homeostasis. Consider two examples: exercise and treatment with atypical antipsychotic drugs. Endurance training has well-established effects on lipid profiles, decreasing LDL and increasing HDL;[89] exercise also suppresses appetite. However, the directionality of this relationship is often unclear. Weight gain and low HDL are also associated with atypical antipsychotic drugs (AAPDs),[90] but do appetite changes, caused by blockade of hypothalamic receptors (e.g., histamine H1 receptor), lead to obesity and thus induce dyslipidemias? Or, rather, do AAPDs affect HDL, precipitating appetite alteration and obesity by interfering with insulin resistance? Cases of either scenario may be found, and additional factors may contribute.[90] Perhaps the soundest conclusion is to assume a normal reciprocity between HDL concentration (or a state it represents) and appetite. As for HDL, do HDL levels directly affect appetite, or are they simply one of many manifestations of metabolic states that also govern production of hunger hormones? Much remains to be learned about the reciprocal relationships of diet, metabolism, and appetite, but the centrality of blood sensing by the brain is clear, as recently illustrated by the finding that hypothalamus tanycytes, which lie outside the blood-brain barrier in the median eminence, support neurogenesis and respond to high fat intake.[91]

Conclusions and Future Studies

Taken together, the studies reviewed here provide the pieces necessary to trace mechanisms of dietary miRNA influence on homeostasis of circulating miRNA profiles. In the most complete model, HDL, a well characterized, diet- and metabolism-related homeostatic system (cholesterol transport) is regulated by miRNA and includes carriers of miRNAs that, when sensed by cellular receptors (e.g., SCARB1), initiate canonical intracellular signaling pathways. Depending on the level and type of signal, this may result in uptake of vehicular small RNA contents into recipient cells as a non-canonical form of signaling—with demonstrated functional consequences and partial depletion of the extracellular miRNA population—or provoke release of additional miRNA vehicles and supplementation of specific portions of the circulating miRNA complement. Furthermore, the HDL system is often deranged in disease. With differential miRNA concentration in HDL vs. cell of origin, disease-associated dietary influence on miRNA profiles could involve apparent up- or downregulation of specific miRNAs, changes that may be only ancillary to pathology. Such miRNAs would not be true disease biomarkers, and manipulating them therapeutically would likely be ineffective.

The findings and syntheses reported in this Point-of-View suggest research directions and precautions that should be taken in ongoing and future miRNA biomarker research (**Table 3**).

It is hoped that further development and research of the xenomiR hypothesis will help to distinguish between directly disease-associated biomarkers and those that result from altered diet quality or quantity. This outcome will allow investigators to focus on specific biomarkers that are also most promising as targets of future small RNA-based therapeutics.[96]

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Table 3. Future directions and considerations in miRNA biomarker studies

Discovery and characterization of additional homeostatic mechanisms	In addition to HDL, other circulating miRNA conveyances should be investigated for involvement in homeostasis of circulating miRNA. These include apoptotic bodies and other large, lipid bilayer-bound microparticles in the range of half a micron to several microns in diameter; microvesicles released from the cell surface (roughly 100–300 nm in diameter);[92-94] exosomes (30–120 nm) that bud into multivesicular bodies before release;[95] lipoproteins other than HDL; and protein complexes that incorporate RNA-binding proteins.[7,8] It should be noted that most of these particles are relatively heterogenous in comparison with HDL.
Animal model research	In contrast with human studies and their large number of uncontrolled variables, animal models allow control of genetic background, type and quantity of diet, and environmental influence. In one important experiment, miRNA profiles from different extracellular fractions (microvesicles, exosomes, HDL) as well as tissue (e.g., liver) should be ascertained in wild type mice fed with plant material or chow containing animal byproducts (incorporation of fresh ingredients would increase the likelihood of intact miRNA uptake). Similarly, plasma and liver miRNA profiles of wild type and knockout mice (e.g., SCARB1, PDZK1 and LDLR) should be compared in the context of different diets. The effects of exogenous HDL particles on appetite should also be monitored in these systems. Throughout, detailed reports of dietary ingredients and intake should be included in animal studies to facilitate interpretation and inter-study comparison.
Human subjects: diet reporting and choice of controls	For miRNA biomarker studies, diet should be added to the list of characteristics that investigators attempt to control for in human subjects research, like age, sex, and race. Detailed information about recent alimentary intake should be recorded for each subject. To the greatest extent possible, studies of diseases that affect diet and weight should be controlled with subjects that display similar food consumption (quantity and type), BMI, and history of weight gain/loss. Activity levels, which affect both appetite and miRNA levels, should also be monitored and reported.
Analysis: appropriate normalization strategies	miRNA profiling researchers must exercise caution in normalization of large data sets, especially when spiked-in controls are used. In several reports of circulating miRNAs in chronic hepatitic C and B in Chinese populations,[101,102] spiked-in plant miR168 or miR156 was used to normalize results. These miRNAs were the most abundant plant xenomiRs in blood from Chinese donors according to Zhang, et al.[38] Depending on the amount of spike-in and the concentration of food-derived plant miRNAs in patient serum, disease-associated nutritive differences (whether as a result of disease itself or socioeconomic patient-to-control differences) could differentially affect the apparent normalized concentration of circulating miRNAs and thus skew results.

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Supplemental Materials

Supplemental materials may be downloaded here:
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