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Mini-Review

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Is Use of Micro-RNA–Containing Food Feasible?

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Abstract

Micro-RNAs (miRNAs) are a class of small non-coding single-strand RNA molecules (22 nt in length) that play an important role in inhibition of translation or degradation of targeted messenger RNAs (mRNAs) by binding 3'-untranslated region (UTR) of target mRNAs. MiRNAs are involved in diverse physiological and pathological processes, including apoptosis, cell proliferation, the cell cycle, carcinogenesis and skeletal muscle function. On this basis, miRNAs can be used to combat disease and maintain health. MiRNAs may also facilitate development of enhanced food or feed. We assessed three factors required for use of miRNAs in food: stability, safety, and efficacy. This review highlights emerging evidence in the use of miRNAs as ingredients in food or animal feed. We also discuss the challenges to, and perspectives for, the application of miRNAs.

Keywords

Micro-RNAs, Anti-sense oligonucleotide (ASO), Mimic nucleotide (mimic), Functional foods

Introduction

Micro-RNAs (miRNAs) are a class of small endogenous non-coding RNAs that bind their target gene through perfect or imperfect base-pair complementarity. The first miRNAs discovered in *Caenorhabditis elegans* by Victor Ambros and Gary Ruvkun [1] were *Lin-4* and *let-7*. *Lin-4* negatively regulates the level of LIN-14 protein by imperfect complementary base pairing with the 3'UTR of the *Lin-14* mRNA. Also, *Lin-4* controls the timing of the development of the first larval stage [2], and post-translational inhibition by miRNA was considered to be specific for nematodes. Surprisingly, *let-7* is not limited to *C. elegans*, rather has been highly conserved through evolution in a range of animal species, including vertebrates, invertebrates and humans [3-6]. These findings suggest that miRNAs are present and functional in a variety of organisms.

Recently, miRNA biosynthesis and processing steps have been revisited. Usually, miRNAs are located in the intron of protein-coding genes and transcribed by RNA polymerase II into pri-RNAs with a 5' cap and poly-A tail. Then, the pri-miRNAs are cleaved to pro-miRNAs by the nuclear microprocessor complex, consisting of RNaseIII (Drosha) and the co-factor DGCR8 (DiGerge critical region 8). Pre-miRNAs are then exported to the cytoplasm by Exportin-5 and further processed. The next processing enzyme, Dicer, an RNase III-type endonuclease, cleaves the hairpins of pre-miRNAs, resulting in double-strand RNA duplexes. They are dissociated by Ago2, which unwinds the double-

stranded RNA duplexes. The mature miRNAs are retained in the RNA-induced silencing complex (RISC) and bind to the 3'-untranslated region (UTR) of target mRNAs to regulate expression. Subsequently, miRNAs regulate mRNA expression by inducing degradation or translational repression [1-8].

Interestingly, the involvement of miRNAs in diverse physiological and pathological aspects has been revealed. For instance, miR-21 functions as an oncogene by regulating many tumor suppressor genes and is upregulated in many human malignancies [9, 10], including breast cancer [11, 12], glioblastoma [13], hepatocellular carcinoma [14], cholangiocarcinoma [15], lung cancer [16], tongue squamous cell carcinoma [17], gastric cancer [18, 19], colorectal cancer [20, 21], and prostate cancer [22]. Moreover, evidence is accumulating that many age-related diseases are also associated with impaired cell signaling cascades. The miRNA control systems linked with the cell cycle, DNA repair, oxidative stress responses and apoptosis are abnormally expressed in mid-life [23, 24]. Two heart-specific miRNAs were deleted in a large proportion of offspring mouse models, which resulted in abnormal heart development [25]. While these lethal effects were expected, another study suggested a subtler role for miRNA in the heart. When miR-208 was eliminated, the mice appeared normal; however, defects were revealed when their hearts were stressed [25, 26]. These results suggest that miRNA studies should be extended to the diagnosis of heart disease. Numerous reports have demonstrated the role of miRNAs in neural development. Evidence for the role of miRNA in Parkinson's disease comes from animal models indicated that loss of miRNAs may be involved in disease development and progression [27, 28]. In cell culture, transfer of small RNA fragments preserved the loss of function in certain miRNA-deficient nerve cells [29, 30]. While these and other results supported an important role for miRNA in neurodegenerative disorders, further work is needed to delineate the exact role of miRNAs in this important area. Recent miRNA deletion studies have revealed a central role in the regulation of the immune response. The deletion of miRNA-155 impaired T and B cell differentiation in germinal centers, and greatly decreased antibody and cytokine production. miRNA-181 and -223 were found to control the T-cell response and granulocyte production, respectively. As more roles for miRNAs in the immune response are found, the list of immune function disorders with a miRNA component will also increase [31-33].

The miRNAs can be transmitted from one species to another, which can result in cross-species regulation of gene expression. Many evidences suggest that food-derived exogenous miRNAs exist in blood and organs of mammals, where they serve functions similar to endogenous miRNAs and simultaneously regulate either multiple target genes or biological processes [34-45]. Thus endogenous miRNAs of one species may influence the biologic functions of another, distantly related species (Figure 1).

Epigenetics can be defined as heritable changes in gene expression that do not involve changes to the underlying DNA sequence, a change in phenotype without a change in genotype [46]. They consist of DNA methylation, histone modifications, RNA interference and chromatin remodeling without alteration of DNA sequence. Epigenetic modifications can be altered by external or internal environmental factors and have the ability to change gene expression. In this context, nutritional epigenetics is important, because food can modify physiologic processes through epigenetic regulation of gene expression [46-48].

However, whether miRNA itself or miRNA-containing food can be included in the human diet or animal feed remains open to speculation.

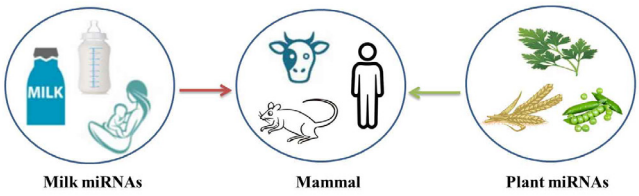

Figure 1: MiRNAs as cross–kingdom regulators.

Ingested miRNAs accumulate in human or animal serum and regulate target gene expression in a sequence-specific manner. In other words, miRNAs in food, including colostrum, mature milk and plants, have a cross-species regulation capability.

Milk and Plant miRNAs

Milk containing miRNAs

Milk contains abundant miRNAs in period of breastfeeding. Hundreds of miRNAs have been discovered by sequencing and microarray analysis in multiplex milks such as bovine [49-55], human [34, 35, 56, 57], rat [60], goat [61], and porcine [62, 63]. Immune-related miRNAs in milk have been speculated to play a crucial role in the development of the immune system in newborn infants [50, 54, 56]. Especially, the MiRNA concentration in colostrum is higher than that in mature milk [49, 50, 64]. Li et al. reported the miRNA expression profiles of lactating and non-lactating bovine mammary glands [55]. Milk miRNAs are stable in harsh environments, such as the digestive tract. In contrast, synthetic miRNAs were degraded at 37 °C, at a low pH (up to pH 1) and by RNase [50, 51]. MiRNAs are packaged in a variety of vesicles, including microvesicles (MVs) and exosomes [51, 53, 54, 57, 65-67]. Such vesicles may allow miRNAs to tolerate degradation in the gastrointestinal tract and be absorbed in the intestine. These coated and/or protected miRNAs could resist the food manufacturing process and be absorbed into the intestine.

Plant miRNAs

MiRNA-containing foods are found in animals and plant resources [68, 69] and dietary miRNA can affect the circulating miRNA profile to regulate the expression of human genes [34, 35, 70-72]. Zhang et al. and Vaucheret reported three important findings [34, 72]. First, some of the plant miRNAs in human serum are genuine plant miRNAs. Also, they were detected in MVs. Second, plant miRNAs were stable in cooked food and could pass through the mouse GI tract. Third, an exogenous plant miRNA, miR-168a, binds to mammalian

low-density lipoprotein receptor adapter 1 (*LDLRAP1*) and decreases the LDLRAP1 protein level. Indeed, the addition of mammalian miR-150 to mice feed downregulated hepatic c-Myb expression of the fed mice. Plant-derived miRNAs (*e.g.*, rice and bean) are stable during food processing, cooking and early digestion (up to 75 min). In contrast, synthetic miRNAs were unstable under identical condition [70]. These findings suggested that vesicles, such as exosome and MVs, can also play a key role in protecting exogenous miRNAs against cooking, food processing and digestion and facilitating their delivery to their target gene.

Cross-Kingdom Activity of miRNAs

Milk-derived miRNAs regulate gene expression in mammals

Colostrum is a complex liquid that provides immunity to the infant and affects maturation of the infant's immune system, particularly the miRNAs in the colostrum [56, 66]. Baier et al. reported that humans absorb biologically meaningful amounts of miRNAs from nutritionally relevant doses of cow's milk [35]. They concluded that miRNAs in milk are bioactive food compounds that regulate the expression of human genes [35]. Melnik et al. suggested a new option for prevention of atopic diseases-addition of physiological amounts of miR-155-enriched exosomes in raw cow's milk to infant formula for mothers incapable of breastfeeding [36]. In contrast, Melnik provided evidence of the pathogenic role of persistent milk signaling in mTORC1- and milk-miRNA-driven type 2 diabetes mellitus [37]. These findings suggest that milk-containing miRNAs regulate mammalian gene expression either beneficially or harmfully.

Plant miRNAs regulate gene expression in mammals

Exogenous plant miRNAs in food regulate the expression of target genes in mammals [34, 38-41]. Zhou et al. and Yang et al. detected plant miRNAs in the sera and tissue of honeysuckle-fed mice [39, 40]. Yang et al. suggested that dietary uptake of MIR-2911 was common in healthy consumers, and reproducible detection of plant-based miRNAs in healthy consumers depended on their dietary abundance (food intake), RNA stability, and digestion [41]. Liang et al. performed a kinetic study of plant miRNAs in human plasma after drinking watermelon juice [42]. Watermelon-derived miRNAs are selectively taken up and some plant miRNAs have a similar concentration as compared with endogenous miRNAs in the plasma. Mlotshwa et al. engineered plant-derived artificial miRNAs that could silence essential human oncogenes and thereby had potential as a cancer therapeutic [43]. Yang et al. and Wagner et al. reported on diverse aspects-including the uptake, delivery, and function-of dietary miRNAs and plant-based miRNAs in mammals [44, 45].

Miravirsen, the First miRNA-targeted Antiviral Drug in Phase 3 Trials

miR-122, known as a hepatitis C virus (HCV)-specific miRNA, is highly expressed in the liver and plays an important role in HCV infection [73-77]. Especially, miR-122 binds to the 5′ untranslated region (5'UTR) of the HCV genome, unlike other miRNA which usually binds to 3' untranslated region of target mRNAs. Then, miR-122 forms an oligomeric miR-122–HCV complex, which not only protects the HCV genome from nucleotide degradation and/or host innate immune responses, but also leads to upregulation of HCV replication in infected liver cells [73-77]. Miravirsen (SPC3649) is a chemically modified anti-miR oligonucleotide and the first anti-miR drug candidate for treatment of HCV infection, which targets miR-122. Locked nucleic acids (LNAs) is a bicyclic RNAs in which the ribose ring is locked by introduction of a 2'-O, 4'-C methylene bridge, resulting the antisense-oligonucleotides (ASOs) showing a high affinity for the target site [78, 79]. Clinical safety and efficacy testing of miravirsen in a phase 2a clinical study has been completed [80]. Miravirsen resulted in a dose-dependent reduction in HCV RNA levels in 36 patients receiving 3, 5, and 7 mg per kg body weight, with the exception of one patient in the 5 mg group and four patients in the 7 mg group. Five patients in the miravirsen groups had side effects of moderate severity, including headache, otitis externa, pelvic bone injury after a fall, syncope and flulike symptoms. Studied of miravirsen have not indicated side effect in animals [80, 81]. However, the only serious side effect was loss of consciousness in one patient [82]. Exogenous and even chemically modified miRNAs can exert a prolonged anti-viral effect. Dangerous side effects that can occur due to the multi-targeting ability of miRNA did not occur except for one patient in the clinical trial. Miravirsen is now preparing a phase 3 clinical trial. Therefore, based on the targeting of miR-122 with miravirsen, design of functional foods containing miRNA antisense or mimic oligonucleotide seems feasible.

Micro-RNAs in Nutrition Act as Epigenetic Regulators

Nutritional epigenetics can modify physiologic processes through epigenetic regulation of gene expression [46-48]. Various nutrients-such as vitamins, methionine, choline, folate, and betaine-can affect DNA modification, and bioactive compounds-including vitamins, fatty acids, curcumin and resveratrol-can regulate the expression of miRNAs [8, 48, 83, 84]. These recent findings suggested that nutrients and bio-compounds in food either directly participate in gene regulation or indirectly affect post-transcriptional regulation by regulating miRNA expression. The nutrients and/or bio-chemicals that regulate miRNA expression are summarized in Table 1. Although research on the relationship between food and miRNA gene expression or regulation is limited, it will be worthy to check the possibility of synergic effect through the combination of meaningful miRNAs as an ingredient of food for human health.

Conclusion and Perspectives

MiRNAs influence cellular processes by regulating their target gene though suppression or degradation. Several

Table 1: Effect of food components on miRNA expression in various human cell lines.

	Upregulated miRNAs	Downregulated miRNAs	References
Vitamin A	let-7a-3, let-7c, let-7d, miR-15a, miR-15b, miR-16-1, miR-107, miR-186, miR-215, miR-223, miR-223, miR-342,	let-7a, miR-17-5p, miR-181b, miR-25, miR-193, miR-195	[91-93]
Vitamin B (folate)	miR-222		[94]
Vitamin D	miR-22, miR-32, miR-98, miR-182	miR-181	[95-99]
Curcumin	miR-22	miR-21, miR-186, miR-199a	[100-102]
Resveratrol	miR-150, miR-663, miR-296-5p	miR-7, miR-17, miR-18b, miR-20a, miR-106a, miR-106b	[103-105]
Ellagitannins	let-7e, miR-370, miR-373, miR-526b, let-7a, miR-29a	let-7a, let-7c, and let-7d, miR-197, miR-373	[106, 107]
Genistein		miR-27a, miR-221, miR-222	[108, 109]
Catechins	let-7a, miR-7-1, miR-16, miR-34a, miR-99a, miR-210, miR-221, miR-330	miR-18a, miR-21, miR-34b, miR-92, miR-93, miR-106b, miR-193b, miR-222, miR-342	[110-113]
Isoflavones	let-7b, let-7e, miR-146a, miR-200b, miR-200c,		[114, 115]
Indol (DIM)	let-7b, let-7e, miR-21, miR-146a, miR-200b, miR-200c		[114, 115]
SCFA butyrate		miR-17, miR-20a, miR-20b, miR-93, miR-106a, miR-106b	[116]
Oleic acid	miR-21		[117]

DIM, 3',3'-diindolylmethane; SCFA butyrate, short chain fatty acid butyrate

miRNAs are specifically up- and/or down expressed in various disease states, research into use of miRNAs as biomarkers or therapeutics is underway. However, there is little interest in use of miRNA in food or animal feed, due to issues such as absorption, degradation during food processing or digestion, and side effects (Figure 2). In this review of dietary miRNA, such as plant miRNAs and milk miRNAs, we confirmed the possibility of their application in food or animal feed. miRNAs stable under harsh conditions (pH 1, RNase, 37 °C) which is associated with their packaging into vesicles, including exosomes and MVs. Conde et al. reported that self-assembled RNA-triple-helix conjugates remain functional *in vitro* and *in vivo*, and that they induce 90% tumor shrinkage in a triple-negative breast cancer mouse model [85]. An RNA-triple-helix structure is created by two miRNAs, an miRNA mimic (tumor suppressor miRNA) and an antagomiR (oncomiR inhibitor). This is a new means of improving the stability of exogenous miRNAs in mammalian systems. In addition, ingested miRNAs can regulate human gene expression. The greatest obstacles in clinical miRNA research are unexpected side effects due to the multi-targeting ability of miRNAs. The phase 2 clinical study of miravirsen, the first miRNA inhibitor drug candidate, reported no serious side effects except for one case and there was no adverse effect in animal testing. A negative or positive relationship between miRNA and nutrients would be an important factor for their use in food or animal feed. As found additional role of nutrients on the indirectly inhibition of the gene via the miRNA, synergic effect between nutrients and dietary miRNA would be also possible. The relationship between foods and miRNAs is highly associated at the epigenetics mechanistic support. Therefore, miRNAs or

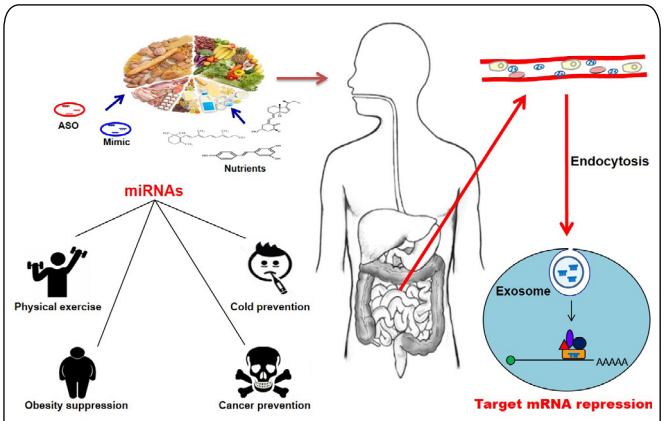

Figure 2: MiRNA-containing food can be designed to regulate specific target genes.

ASO and/or mimic of miRNAs associated with specific disease enable exogenous control in the body. The high-tech level functional food can be achieved by combining several core mi-RNAs mimics or antisense oligonucleotides that can selectively suppress target gene expression under physiologic conditions. Core miRNAs involved in various processes such as physical exercise [86, 87], cough prevention or release [88], obesity [89, 90], and cancer prevention [8] would be effective resource for food or animal feed. We can apply not only mimics of the core miRNAs as tumor suppress gene but also ASO of core miRNAs as oncogene with combination strategy. Packaging of artificial ASO and/or miRNA mimics within exosomes maintains their stability during digestion. MiRNA-containing foods are absorbed in the intestine and the miRNAs delivered to the bloodstream. Endocytosis of the exosome results in delivery of miRNAs and regulation of the expression of their target genes. Use of miRNAs in food may be an effective method of disease prevention by synergic combination of miRNA modulation and phytochemicals. For example, miRNA mimics that suppress expression of cancer-causing genes are packaged in vesicles, and biologically meaningful amounts of packaged miRNAs can be added to food. Use of such combinations of common miRNAs will facilitate development.

miRNA-containing biomaterials (ASO or mimics) may be useful function food ingredients to prevent and treat various diseases.

Conflict of Interest

The authors do not have any conflict of interest regarding this mini-review.

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Authors Contributions

Jin-Wook Kang and Hyun-Ah Baek are contributed equally to this work.

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