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Editorial

Xeno-miRs and Circulating miRNAs as Novel Biomarkers in Certain Diseases

Gülsüm Deveci [1], Raffaele Capasso [2] and Duygu Ağagündüz [1,*]

[1] Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, 06490 Ankara, Turkey
[2] Department of Agricultural Sciences, University of Naples Federico II, 80055 Portici, Italy
* Correspondence: duyguturkozu@gazi.edu.tr

1. miRNAs

MicroRNAs (miRNAs) are non-coding RNAs consisting of a length of roughly 22 nucleotides that participate in gene regulation. Mature miRNAs have been identified in more than 3000 species, ranging from plants to humans [1]. These miRNAs, which are involved in the regulation of gene expression, have been preserved throughout evolution. miRNAs regulate fundamental cellular and biological functions, such as proliferation, apoptosis, and development [2]. miRNAs control post-transcriptional gene expression through this regulation. miRNAs are able to influence epigenetic mechanisms by targeting key enzymes involved in the creation of epigenetic memory [3].

The endogenous coding process of miRNAs takes place in the genome. The process starts with DNA being transcribed into pri-miRNAs by RNA polymerase II. Pri-miRNAs are then transformed into pre-miRNAs by Di George syndrome critical region 8 gene (DGCR8) and RNase III Drosha. The resulting pre-miRNAs are transferred to the cytoplasm by exportin 5 and Ras-related nuclear protein (RAN)-GTP factors. In the cytoplasm, RNase III Dicer causes miRNAs to divide and combine with RNA-inducing silencing complex (RISC, miRISCs), thus forming mature miRNAs [4,5]. The miRISC that interacts with the nucleus may be involved in the miRISC:mRNP complex as it exits the nucleus. miRISCs can combine with polysomes in the cytosol, or interact with mRNAs in the granular endoplasmic reticulum. miRISCs can also localize to mitochondria. As a result of the localization of miRISCs in the Golgi, vesicular or non-vesicular miRISCs can be exocytosed into the extracellular environment in order to mediate intercellular communication. This constitutes evidence that miRNAs can be released into extracellular fluids [6]. Potential carriers of miRNAs to the extracellular environment can be classified into three groups. These are (i) miRNA-carrying exosomes or micro-particles mediating cell-to-cell communication, (ii) vesicular carrier apoptotic bodies other than exosomes, and (iii) some proteins such as nucleophosmin1 (NPM1), HDL, and Argonaute (AGO)-2 [7]. The stages of endogenous and exogenous miRNA synthesis and secretion are summarized in Figure 1.

miRNAs binding to protein-coding mRNAs may cause a decrease in target protein expression [8]. In addition, tissue-specific miRNAs can also be detected in body fluids and play a role as promising biomarkers in pathological conditions such as cancer [9]. Furthermore, miRNAs are associated with the molecular mechanisms of various clinical conditions (angiogenesis, nervous system and immune system modulation, gastrointestinal diseases, autoimmune diseases, and some chronic diseases such as diabetes, etc.) and modulate every aspect of cell activity, including cell differentiation, cell metabolism, cell proliferation, apoptotic cell death, and tumor formation [10].

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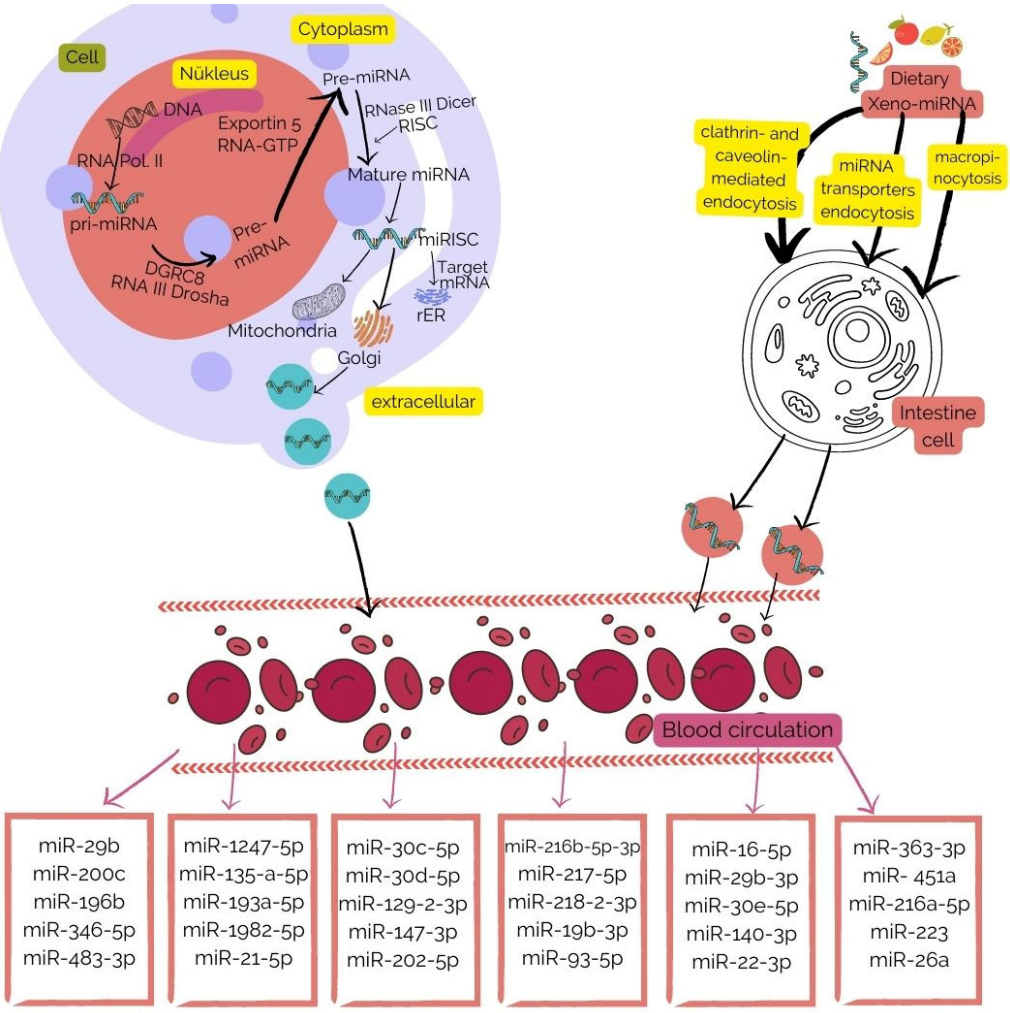

Figure 1. Schematic summary of endogenous miRNA synthesis and the incorporation of dietary xeno-miRNAs into the organism and circulation.

2. Dietary Xeno-miRNAs

Xeno-miRNAs are exogenous miRNAs, mostly of dietary origin, detected in host biofluids. In this context, it is reported that the number of xeno-miRNAs is quite high in some foods and edible plants [11]. These foreign miRNAs are present in human body fluids, can be transferred to the circulatory system, and, thus, can be used as biomarkers [11,12].

miRNAs of dietary origin, which may have an impact on mammalian physiology, are of particular interest. Some mechanisms by which xeno-miRNAs of dietary origin (especially xeno-miRNAs of plant origin) can be involved in organisms through dietary means in a free form, encapsulated in exosome-like nanoparticles, or involved in mechanisms associated with proteins are discussed. These possible mechanisms are (i) uptake of xeno-miRNAs by intestinal epithelial cells via molecules such as transmembrane miRNA transporters or receptor-mediated endocytosis; (ii) uptake of xeno-miRNAs via mechanisms such as extracellular vesicles, phagocytosis, pinocytosis, and clathrin-or-caveolin-mediated or independent endocytosis; (iii) packing of xeno-miRNAs into microparticles after entry into intestinal epithelial cells; (iv) xeno-miRNAs forming proteinase K-resistant complexes during digestion and absorption; (v) immune system cells capturing miRNAs in the intestinal lumen and releasing them into the bloodstream; and (vi) xeno-miRNAs spreading paracellularly across intercellular spaces between intestinal barriers [13] (Figure 1).

More evidence on the xeno-miRNA contents of certain foods is brought to light as time goes on [14]. In this context, miR-148a-3p, miR-30a/d-5p, miR-22-3p, miR-146b-5p, miR-200a/c-3p, and let-7 found in the cell, lipid, and skim milk fractions of human breast

milk, the first food consumed in the first years of life, are among the first ten miRNAs found to be contained in this food [15]. The ability of these miRNAs to modulate the immune capacity of infants is of importance. This ability plays an important in understanding the basics of nutrition and communication between organisms [16]. miRNAs of plant origin can also play an important role in human health. Some plant miRNAs such as miR-156, miR-168a, and miR-172a target host cell mRNA following in vivo absorption, inhibit the post-transcriptional splicing or translation of target mRNA, and affect protein expression [17,18]. In addition, according to the review study conducted by Wagner et al. (2015), pork (*sus scrofa*) has a high content of miR-1, while poultry (*gallus gallus*), wheat (*triticum aestivum*), barley (*hordeum vulgare*), maze (*zea mays*), and rapeseed (*brassica napus*) have high contents of miR-206, miR-156a, miR-168-5p, miR-319b, and mir-156, respectively [19]. Foods of animal origin often have high contents of miRNA, while dairy products, especially cheese varieties, are reported to have the lowest contents of miRNAs among these foods [20].

3. miRNAs and Their Functions and Potential Uses in Diseases

Different cell types have different miRNA expression profiles, and cell/tissue/organ-specific miRNAs (or profiles) may indicate different diseases. Circulating miRNAs are either actively secreted by living cells or passively released due to cell death [21]. Some types of extracellular miRNA serve an intercellular signaling function during various physiological and pathological processes [22]. miRNAs have been detected in serum and plasma. Circulating miRNA profiles are associated with a number of different tumor types and conditions such as stroke and heart disease, as well as changing physiological conditions such as pregnancy [23]. For example, circulating miR-208b is used as a highly sensitive and selective disease-specific biomarker of heart disease [24]. People with pulmonary hypertension, which plays an important role in the pathogenesis of heart failure, show decreased circulating miR-451 and miR-1246 levels and increased circulating miR-23b, miR-130a, and miR-191 levels. A significant decrease in the level of miR-1, miR-26a, and miR-29c in these people has potential diagnostic significance, while miR-21, miR-130a, miR-133b, miR-191, miR-204, and miR-208b are used as biomarkers of this disease [25]. The expression levels of miR-208a, miR-21, and miR-208b, which change significantly during the pathological progression of myocarditis, are significantly correlated with an improvement in left ventricular function. These miRNAs are becoming important in the diagnosis, treatment, and follow-up of children with myocarditis [26]. In patients with type 2 diabetes mellitus, the serum levels of miR-122, miR-192, miR-194, and miR-215 are high, and high serum levels of miR-192 and miR-194 are associated with the disease independently of fasting glucose, HbA1c, and other risk factors. Circulating miR-192 and miR-194 are potential biomarkers for risk of diabetes [27]. miRNAs that affect various parts of insulin signaling in the pancreas, liver, muscle, and adipose tissue have been identified. miR-124a and miR-34a are involved in pancreatic development (through their effects on forkhead box protein O2 (FOXO2), Ras-related protein (RAB27A), vesicle-associated membrane protein 2 (VAMP2) and B-cell lymphoma 2 (BCL-2)). Adipose tissue is an important source of circulating exosomal miRNAs and contributes different exosomal miRNAs from different fat stores to the circulation. Many circulating miRNAs, such as miR-16, miR-101a, miR-21, miR-299, miR-200c, miR-467b, miR-186, miR-877, and miR-30c-2, are associated with adipogenesis [28]. miR-33A and miR-33b, in tandem with sterol regulatory element-binding protein (SREBP) transcription factors, have a very important role in the control of cholesterol and lipid metabolism. Other metabolic miRNAs such as miR-103 and miR-107 regulate insulin and glucose homeostasis, while miRNAs such as miR-34a are the main regulators of hepatic lipid homeostasis [29]. miRNAs characterized as biomarkers in some non-infectious diseases and clinical conditions, their possible functions, and their effects on genetic expression are summarized in Table 1.

Table 1. miRNAs characterized as biomarkers in some non-infectious diseases and clinical conditions, their possible functions, and their effects on genetic expression.

Disease	Type of miRNA	Function	Up/Down-Regulate	Reference
Stage IIIb or IV lung adenocarcinoma	miR-25, miR-145 and miR-210	Biomarkers in predicting the effectiveness of pemetrexed treatment	-	[30]
Stomach cancer	miR-17-92	Markers in the prognosis of advanced stomach cancer and the effectiveness of chemotherapy	Plasma miR-17-92 in advanced stomach cancer ↑, ↓ after chemotherapy Plasma miR-17-92 in chemo-resistant patients ↔	[31]
Prostate cancer	miR-205 miR-214	Diagnostic biomarkers	Tissue miR-205 and miR-214 ↓	[32]
Type 2 diabetes mellitus	miR-150 miR-30a-5p miR-15a miR-375	Diagnostic marker of prediabetes	miR-150 and miR-30a-5p ↑ miR-15a and miR-375 ↓	[33]
Type 2 diabetes mellitus	miR-155	Marker of pathogenesis and metabolic control	miR-155 ↓	[34]
Aging and Type 2 diabetes mellitus	miR-146a	Marker utilized through the detection of circulating miRNA	miR-146a with aging ↓ miR-146a with aging in T2DM patients ↓ miR-146a in T2DM patients treated with metformin ↑	[35]
Acute myocardial infarction	miR-122-5p/133b ratio	Prognostic biomarker	-	[36]
Acute heart failure	miR-16-5p miR-106a-5p miR-223-3p miR-652-3p miR-199a-3p miR-18a-5p	Relationship with biochemical pathways in heart diseases (CRP, creatinine, growth differential factor soluble ST-2, procalcitonin, galectin-3)	-	[37]

Table 1. *Cont.*

Disease	Type of miRNA	Function	Up/Down-Regulate	Reference
Coronary artery disease	miR-34a	Expression in endothelial progenitor cells	miR-34a ↑	[38]
Chronic obstructive pulmonary disease (COPD)	miR-489-5p	Early detection biomarker and therapy tool	miR-489-5p ↓	[39]
Pneumonia	hsa_circ_0018429 hsa_circ_0026579 hsa_circ_0125357 hsa_circ_0099188	Sensitive and specific biomarker for diagnosis	-	[40]
Liver cirrhosis	miR-106b miR-181b	Sensitive and specific clinical diagnostic biomarker at early stages	-	[41]
Hepatitis B Virus (HBV)	miR-375	Early predictive marker in the prognosis of hepatocellular carcinoma due to HBV-associated hepatitis or cirrhosis	Serum miR-375 ↓	[42]
Alzheimer's disease	let-7b let-7e	Indicator of neuropathological pathways	Cerebrospinal fluid let-7b and let-7e ↑	[43]
Parkinson's disease	miR-34a-5p	Diagnostic biomarker	miR-34a-5p in small extracellular vesicles free of exogenous protein contaminants ↑	[44]
Down syndrome	miR-155 miR-125b	Down syndrome treatment	miR-155 and miR-125b in tonsillar β cells ↑ Plasma miR-125b ↑	[45]
Duchenne muscular dystrophy	miR-206 miR-1 miR-133	Monitoring of prognosis and alternative non-invasive biomarker	Serum miR-1 and miR-206 ↑	[46]

↑: increased, ↓: decreased, ↔: not changed.

In addition to their use as biomarkers, miRNA-based therapeutics are an emerging field that shows significant promise. Studies in mice and non-human primates and early trials in humans clearly show that there is a potential to utilize miRNAs as valuable therapeutics. miRNAs such as miR-21 and miR-122 appear to be localized regulatory

molecules designed to exert global modulation through moderating effects on a large number of targets [47].

4. The Effects of Diet on miRNAs

It is suggested that miRNAs of food origin are bioavailable and influence gene expression in mice and humans [48]. Food, nutrients, or non-nutrient compounds can affect the expression of circulating miRNAs and change their tissue expression and plasma levels [49].

Most bovine miRNAs have nucleotide sequences that complement human gene transcripts, suggesting that miRNAs in milk may modulate human genes. It was observed in postprandial concentration time curves that significant amounts of miR-29b and miR-200c were absorbed, while plasma concentrations of miR-1 did not change [50]. Plasma miR-29b and miR-200c levels increase due to milk consumption [48]. Some miRNAs are involved in regulating molecular pathways related to cardiovascular diseases. miRNAs and target genes involved in these pathways are modulated by diet. Choline, betaine, and L-carnitine, nutrients found in animal products, are metabolized to trimethylamine n-oxide (TMAO), which is associated with risk of cardiovascular disease (CVD). Dietary TMAO intake increases the expressions of miR-21-5p, which has a well-known role in inflammation, and miR-30c-5p, which is involved in lipid metabolism [51]. A study investigating intestinal miRNAs, which have a potential role in the regulation of lipid metabolism, shows that miRNA expressions are altered in both the liver (miR-30d-5p, -129-2-3p, -147-3p, and -202-5p) and the colon (miR-30d-5p, -129-2-3p, -202-5p, -216b-5p-3p, -217-5p, and -218-2-3p) following lipid intake. According to this study, miR-218-2- 3p expression in the duodenum and jejunum in males increased significantly at the second hour following dietary lipid intake and returned to basal values at the fourth hour following dietary lipid intake, while the level of expression remained constant in females. Two hours after dietary lipid intake, miR-138-1-3p levels were significantly increased in the jejunum in males, and miR-129-2-3p levels were increased in the duodenum in females [52]. This suggests that the sex factor may cause differences in the expression of the same miRNA.

Among nutrients, vitamins play a role in the modulation of miRNA profiles, in health, and in diseases. These micronutrients can regulate the expression of gene products through the modulation of transcription and translation. In the case of vitamin D deficiency, the risk of fatal prostate adenocarcinoma increases, and especially in older men. The active form of vitamin D binds to vitamin D receptors and regulates the gene expressions of miR-126-3p, miR-154-5p, and miR-21-5p. Both miR-154-5p and miR-126-3p have a positive correlation with $1,25(OH)_2D$ levels. Ribonuclease III (DICER 1), used in the formation of mature miRNAs, is expressed abnormally in prostate adenocarcinoma lesions. DICER1 levels also increase with increases in $1,25(OH)_2D$. An increase in DICER may contribute to a reduced risk of prostate-specific antigen recurrence [53]. In addition, intake of multi-B vitamins (B1, B2, B3, and B9) increases cognitive performance by reducing hsa-miR-34a-5p, hsa-miR-128-3p, hsa-miR-181a-5p, and hsa-miR-204-5p expressions [54].

Minerals, another micronutrients, are involved in many metabolic processes. Minerals act as a cofactor for enzymes involved in DNA replication, gene transcription, and protein synthesis. Selenium, which is among these essential minerals, and coenzyme Q10 play important roles in processes from the fetal period to old age [55]. Selenium and coenzyme Q10 supplementation in the elderly causes a decrease in cardiovascular mortality and inflammation markers. Furthermore, miRNA analyses can provide important insights into the mechanisms behind the clinical effects of this supplementation. Selenium and coenzyme Q10 are essential for important cellular functions. The intake of selenium and coenzyme Q10 cause changes in miRNA expressions. Following intake of selenium and coenzyme Q10, miR-19b-3p, miR-93-5p, miR-16-5p, miR-29b-3p, miR-30e-5p, miR-140-3p, miR-22-3p, miR-363-3p, and miR-451a expressions increase, while miR-199a-3p, miR-26a-5p, miR-199a-5p, miR-221-3p, miR-151a-5p, miR-151a-3p, miR-130a-3p, miR-30c-5p, miR-191-5p, and miR-125a-5p expressions decrease [56]. Selenium is an important micronutrient for fetal development. miRNAs play an important role in the function of the placenta and

communication between the placenta and maternal systems. Selenium uptake during the prenatal period shows that miR-216a-5p is a miRNA that has a relationship with selenium. This finding can give clues about maternal and fetal nutrition [57]. In addition, minerals are part of antioxidant enzymes [58] and mediate gene expression. Plasma levels of minerals [59,60] affect the expression of miRNAs that serve as biomarkers [61]. Zinc finger proteins are involved in the processes of cell cycle progression, DNA repair, transcription, and miRNA degradation. Zinc dinger SWIM-type containing 8 (ZSWIM8), which has a zinc finger SWIM region, is involved in target-directed miR-7 degradation [62]. In addition to normal physiological processes, zinc also alters miRNA expressions in cases of pathology. Decreased zinc levels are observed in prostate cancer tumors, accompanied by decreased expression of zinc transporters. A miRNA group is identified to regulate zinc transporters. Of these, miR-183, miR-90, and miR-182 are overexpressed in prostate cancer tissue and suppress zinc transporters. Although it is thought that an increase in dietary zinc decreases the risk of this type of cancer and related deaths, the results are not conclusive [61].

5. Conclusions and Recommendations

The results of the conducted studies show that miRNAs, which are among non-coding RNAs, can directly regulate gene expression and that food and nutrients can affect the transcription, translation, and epigenetic mechanisms in this process. The most important exogenous sources of miRNA are dietary xeno-miRNAs. These circulating miRNAs increase plasma levels and change the expression of mRNA and protein in tissues. In addition to their modular effects on protein expression and the immune system, it is also predicted that various miRNAs can be used as markers in the diagnosis and prognosis of non-infectious diseases, such as type 2 diabetes mellitus, coronary artery disease, neural degenerative diseases, and cancer. However, there seems to be a long way to go for the involvement of miRNAs in treatment processes.

It is recognized that extracellular/circulating miRNAs not only serve as biomarkers of diseases but can also play important roles in intercellular communication. The interaction of endogenously synthesized miRNAs with xeno-miRNAs affects the balance on the scales of health and disease. While some of the studies included in this article study the effect of nutrients on endogenous miRNAs, they mostly evaluate the effect of nutrients alone. However, the foods in our diet are a matrix consisting of nutrients and non-nutrient compounds. In addition, dietary variances, the duration of the studies, and some individual factors related to the participants cause differences in xeno-miRNA uptake and endogenous miRNA expressions. It is recommended that future studies investigate the interaction between these genetic biomarkers and diseases while taking these factors into account.

Furthermore, despite the above-mentioned current information, the effects of xeno-miRNAs taken through nutrition on the organism, and especially on genetic expressions, are among the issues that need to be investigated further. In particular, there is a need for randomized, controlled clinical trials, especially on the presence of interactions with miRNAs and/or whether the possible effects detected are biologically significant.

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