

MicroRNAs and Nutrition

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Micro RNAs (miRNAs) are a small noncoding RNA molecule with 19 to 25 nucleotides (nt) long. Despite the fact that miRNAs are not translated into proteins, their regulatory roles in gene expression make them extremely significant. Studies emerged that more than %60 of the protein-coding genes are regulated by miRNA. This data provides insight into the different effects of miRNA on molecular and, as a result, physiological functions. Several clinical trials have shown that mutations in miRNA and knockout of miRNA regulatory functions have significant consequences. This is very related to the fact that miRNA is extremely conserved among species.^[1,2] Animal miRNA at the molecular level, regulates the gene expression by targeting the 3' untranslated region (UTR) of messenger RNA (mRNA). miRNA has a sequence called 'seed region' in its 5' end and that is the vital sequence that is needed for targeting the mRNA. It is known that a single miRNA molecule can target and influence hundreds of mRNA molecules.^[3] miRNA molecules bind to the targeted mRNA by simply Watson-Crick base pairing. Functions of miRNA in the cell vary both in the nucleus and the cytoplasm, with diversified mechanisms of gene regulation. miRNA can silence a gene or can activate a gene. miRNA is

ABSTRACT

A micro RNA (miRNA) is a small noncoding RNA molecule with highly conserved regions among species. miRNA is responsible for gene silencing through targeting messenger RNA (mRNA). More than 60% of the proteins coded by the human genome are said to be regulated by miRNA. Since miRNA has so many functions, its dysregulation causes a variety of diseases. With the progress of nutriepigenomics, the relationship between diet and epigenetic regulation factors like miRNA is becoming clearer every day. Many natural compounds have been shown to influence miRNA expression in studies. Polyphenols are the most investigated chemicals that have a positive or negative impact on miRNA expression. The use of natural compounds to regulate miRNA is a promising therapeutic agent. While miRNA was once thought to be only synthesized endogenously, it is now thought that miRNA can be obtained from dietary sources such as cow milk and rice. Food-based miRNA consumption is crucial for unlocking new possibilities in miRNA control and disease treatment.

Keywords: microRNA, nutrition, polyphenol.

thought to have a role in almost all types of cancer in humans, and most probably in other diseases. After numerous studies, now it is acknowledged that miRNA is an important potential biomarker for cancer diagnosis.^[4]

miRNA was known to be an endogenous RNA that is only synthesized by the organism itself. Nevertheless, it is revealed that miRNA can be obtained from dietary sources.^[5] Additionally, it is now known that nutrients that are taken up from dietary sources may have an influence on the expression levels of miRNA.^[6] The aim of this review is to take a closer look at the relationship between miRNA and nutrition, as well as the effects these relationships have on human diseases. Biogenesis of miRNA will also be focused on for better understanding of miRNA expression changes and bioavailable miRNA.

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miRNA BIOGENESIS

The endogenous miRNA is produced with the help of a complex of enzymes in both plants and animals. Reciprocally to its evolutionary conservation, the process of miRNA biogenesis varies among plants and animals. 80% of the miRNA genes are placed in the intronic regions of the animal genome. In plants, 90% of the miRNA is transcribed from the exonic regions, as they are independent transcriptions. Through the studies both in humans and *Arabidopsis thaliana*, it is revealed that splicing and alternative splicing are crucial processes for regulation of miRNA biogenesis.^[7]

In animals, primary miRNA (pri-miRNA) is produced first, as shown in Figure 1. This is mostly performed with RNA pol II. pri-miRNA can be transcribed from single miRNA gene (monocistronic), miRNA gene clusters (polycistronic), or intronic regions. pri-miRNA is then transformed into precursor miRNA (pre-miRNA) which is hairpin structured. The process of pre-miRNA formation from pri-miRNA includes RNase III, Drosha enzyme, double-stranded RNA (dsRNA) binding protein, and finally DiGeorge syndrome critical region 8 (DGCR8). This enzyme complex is collectively called Drosha. To export the pre-miRNA to the cytoplasm, exportin 5 (XPO5)

protein takes place. Then, in the cytoplasm, a protein complex involving RNase III and Dicer processes pre-miRNA to form a miRNA duplex. Finally, Argonaute (Ago) proteins are involved in its slicing activity and cleavage of the miRNA duplex. The miRNA strand that is left forms the RNA induced silencing complex (RISC).^[8]

MODULATION OF miRNA AND NUTRITION

Diet is considered a major environmental factor for human health, since it is somehow related to almost all physiological and cellular functions. The expanding study, epigenetics, is the study of heritable modifications on DNA and chromosomes without any change in the DNA sequence. Epigenetic research includes the regulators of gene expression, such as miRNA. Nutriepigenomics is the combined study of epigenetics and diet. Diet may affect various molecular functions, such as the functions of miRNA. It is found that miRNA expression levels may be influenced by nutrients such as vitamins, fat, protein, hormones.^[9]

Besides that, most of the findings are on the interactions of polyphenols and miRNA. Before their effects on miRNA, polyphenols were already

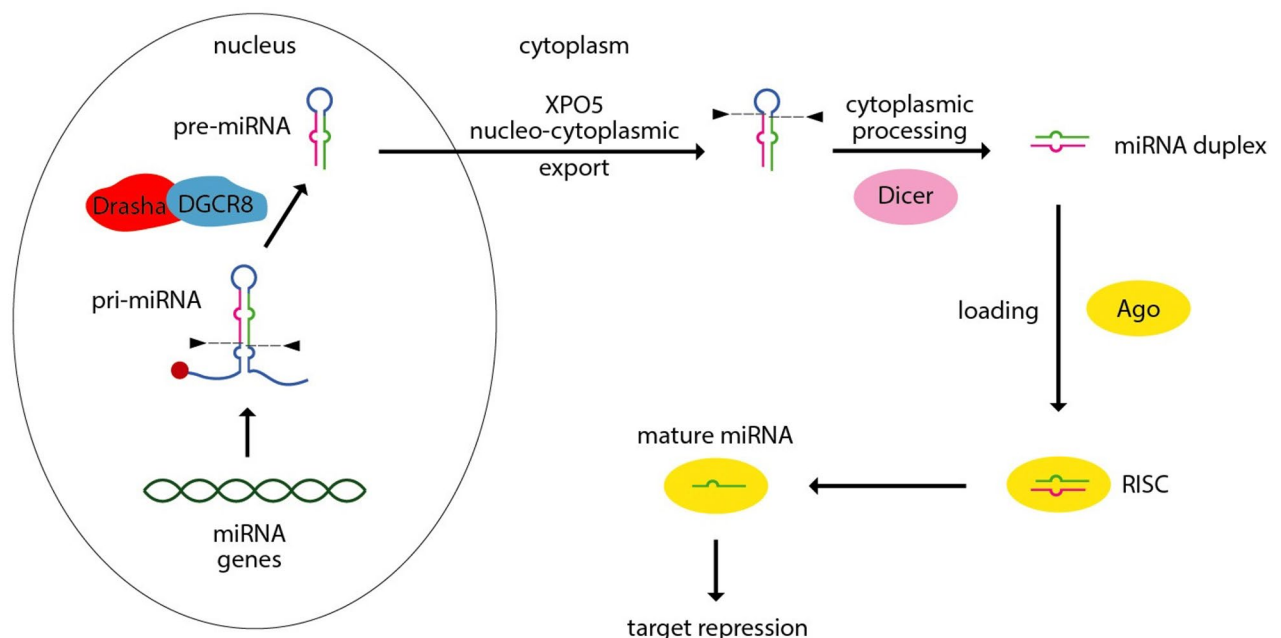


Figure 1. A generalized scheme for the biogenesis pathway of miRNA in animals. The process can be divided into 5 steps as primary miRNA transcription, Drosha involvement in the nuclear process, export from nucleus with XPO5, DICER involvement in cytoplasmic process, and finally the formation of RISC involving Ago proteins in the cytoplasm. The figure is adapted from Matsuyama H and Suzuki HI, 2019.^[8]

known and studied for their roles in cardiovascular diseases, neurodegenerative disease, and also cancer. Polyphenol is a class of natural chemicals, and it has a wide range of dietary sources such as fruits, vegetables, cereal, and even beverages like tea, coffee, wine. It is said that more than 500 polyphenols are found in foods. Polyphenols consist of subclasses such as flavonoids, stilbenes, lignans, phenolic acid, and specific curcuminoids. Quercetin is one of the certain polyphenols that is studied. For humans, the average dietary polyphenol amount that is taken is 1 g.^[10]

CURCUMIN AND miRNA

Curcumin is the major component of the turmeric (*Curcuma longa*) plant, and it is a bioactive polyphenol with significant roles as antibiotic, anti-cancer, anti-aging agents. Turmeric is a widely used spice, especially in India and the rest of Asia, for the preparation of curries.^[11] In 2014, a study with isolated breast cancer cells from humans showed that curcumin positively regulates some miRNA molecules, including miR181b. Also, overexpression of miR181b is suggested as an inhibiting factor for breast cancer metastasis with an in vivo research in immunodeficient mice. Curcumin affects the miRNA and therefore affects the inhibition of metastasis. miRNA that is related to metastasis are called 'metastamirs'. There are also studies that support the effect of curcumin on tumor cells and tumor microenvironment through regulation of miRNA expression.^[12] Further research revealed more interaction between curcumin and miRNA expression. It is found that curcumin intake regulates even more oncogenic and tumor suppressor miRNAs, and they are listed as upregulated miRNAs with the intake of curcumin (miR-21, miR-17-5p, miR-20a, and miR-2) and downregulated miRNAs with the intake of curcumin (mir-34a/c). These miRNAs are known to have a role in tumor initiation, growth, and metastasis.^[13] Such mechanism to this interaction is that curcumin upregulates mir-15a and mir16 in MFC7 cells, which then reduces Bcl-2 (B-cell lymphoma 2) expression and causes cancer cell death. Another correlation to the anti-cancer effect of curcumin is the upregulation of mir-34a. Again in mice, inhibition of metastasis by upregulation of mir-181b and therefore downregulation of pro-inflammatory proteins is indicated in curcumin consumption. One example of miRNA dysfunction is that the miR-19 targeted axis of PTEN/AKT/p53 proteins is dysregulated in the effect of Bisphenol A (BPA), a plastic derivation, therefore carcinogenesis

is promoted. An interesting result is that curcumin reverses this and inhibits the cancer-promoting effect.^[14] In relatively newer research, curcumin effect on osteogenesis via overexpression/inhibition of mir-126a-3p is shown. According to that research, this mechanism via intake of curcumin, then promotes some other pathways, and finally bone mass decreases with osteogenesis suppression. Scientists considered curcumin as a potential threat for tumor metastasis in this situation.^[15] Curcumin may upregulate or downregulate miRNA molecules; different amounts of curcumin may result differently in the same model organism, and each situation may be followed by different pathways. These pathways and their correlation with breast cancer, nasopharyngeal carcinoma (NPC), lung cancer, and more diseases are indicated with recent studies.^[16,17]

QUERCETIN AND miRNA

Quercetin is a polyphenol from the flavonoid subgroup, and it is a biologically active chemical.^[18] Quercetin is a bioavailable molecule that is mostly taken up with apples, grapes, onions, broccoli, and tomatoes. Quercetin is known and researched for its anti-carcinogenic properties, as a group of scientists found that a quercetin-rich diet decreases the risk for lung cancer. One of the mechanisms for the anti-carcinogenesis effect of quercetin is based on miRNA modulation.^[19] In 2012, one of the earliest studies on the topic focused on anti-inflammatory effects of quercetin. In this study, mice are fed a quercetin-rich diet. As a result, it is found that inflammatory genes are less expressed than normal with quercetin. How this mechanism works is that hepatic miR-125b and miR-122 are found upregulated by quercetin which then suppresses the inflammatory response pathway.^[20]

Another study is performed with lung adenocarcinoma patients. Claudin-2 was known as a biomarker since it is highly expressed in lung adenocarcinoma tissues. Discovery from study is that quercetin upregulates miR-16 and therefore Claudin-2 mRNA stability is decreased. These molecules are suggested as potential therapeutic targets for adenocarcinoma.^[21] Quercetin also upregulates miR let-7c and this pathway decreases the tumor growth in pancreatic cancer patients.^[22] Quercetin is found to suppress osteosarcoma metastasis through the regulation of miRNA.^[23] Furthermore, quercetin is studied in several cancer types in humans, and it is related to upregulation of miR let-7a, miR let-7c, miR-142-3p, and miR-200b-3p in pancreatic

cancer. miR-16, miR-217 and miR-145 are also found to be regulated by quercetin in ovarian cancer, lung cancer, and osteosarcoma tissues. Quercetin is an important nutrient and its effect on miRNA expression is still being studied.^[24]

EPIGALLOCATECHIN-3-GALLATE AND miRNA

Epigallocatechin-3-gallate (EGCG) is a polyphenolic catechin, a natural compound that is the dominant constituent of green tea (*Camellia sinensis*). Studies on EGCG revealed its anti-infective properties. The demonstrated antiviral effects of EGCG include the EGCG activity against human immunodeficiency virus (HIV), influenza A, and hepatitis C.^[25] In 2011 scientists examined the cells from both human and mouse lung cancer tissue. For the first time, EGCG is found to target and upregulate miR-210 specifically. Upregulation and therefore overexpression of miR-210 is shown to reduce cell proliferation in pancreatic cancer cells and esophageal squamous cell carcinoma. According to this research, EGCG is a promising therapeutic agent.^[26] In a study, 21 miRNAs whose expressions are mediated by EGCG are identified. Those miRNAs are all related to important pathways of carcinogenesis.^[27] EGCG upregulates another miRNA; miRNA let7-b in melanoma tissues. The upregulation of miRNA let7-b induced by EGCG, then causes a down regulation of a target gene which is related to tumor progression.^[28] It is shown that EGCG mediated regulation of miRNA suppresses cervical cancer.^[29] More recently, EGCG is found to be a suppressor for tumorigenesis and cell growth in breast cancer. The mechanism for this includes the downregulation of miR-25 expression in breast cancer MCF-7 cells. They found that the bioactivity to regulate miR-25 requires at least more than 0,5µg/ml of EGCG concentration.^[30] EGCG and miRNA regulation are found to be related to various diseases, most importantly cancer. Nasopharyngeal carcinoma (NPC) is one of the following subjects that has been searched. EGCG is considered a potential therapeutic agent in many cancers.^[31]

RESVERATROL AND miRNA

Resveratrol is a polyphenol compound that is found abundant in grapes, berries, wine, and peanuts has many activities against neurodegeneration, oxidative stress, inflammation, glycation, cancer, and aging. Somehow, resveratrol has low bioavailability, which means it is not easily taken from foods.^[32]

It is acknowledged that resveratrol is an effective treatment through its regulatory function on miRNA. These effects of miRNA regulation by resveratrol on diseases such as cancer are confirmed with more than one hundred scientific papers.^[24] Resveratrol has been found to regulate neurodegeneration-related miRNAs. A group of miRNA is known as upregulated in neurodegenerative diseases. According to the studies, resveratrol has shown a neuroprotective effect as it regulates these miRNAs. They found that resveratrol-mediated regulation of miRNAs may even prevent Alzheimer's Disease (AD).^[33] A study that is performed with mice showed a decreasing effect of resveratrol on allergic asthma, which is a chronic inflammatory disease. Here, resveratrol significantly downregulates miR-34a and therefore attenuates asthma.^[34]

Resveratrol bioactivity is also studied in colon cancer in which it downregulates certain oncomiRs such as miR-17, miR-21, miR-25, miR-92a-2, miR-103-1, and miR-103-2. Resveratrol decreases miR-221 expression in melanoma and in prostate cancer. It also upregulates miR-200c in lung cancer. Certain miRNAs are regulated by resveratrol in breast cancer. Upregulation or downregulation of miRNA has various roles in each physiological and pathophysiological system.^[24]

However, the exact mechanism of the relationship between the nutrients and miRNA expression or other epigenetic factors is not completely established yet. According to a study that is focusing on the intake of 23 natural compounds (lipids, micro-elements, and vitamins) and performed with 120 volunteers show that vitamin D, vitamin E, and sodium affected the highest number of miRNAs.^[35]

DIETARY miRNA

It is evident that miRNA is not only synthesized endogenously, but can be taken up from dietary sources. There are at least 15 known dietary miRNA sources, all of which are linked to a variety of physiological and pathological functions. It is proved with studies that the amount of miRs absorbed from nutritionally relevant amounts of foods is sufficient to elicit biological effects. miRNAs are bioavailable after encapsulated in the cell in which it is synthesized. miRNA encapsulation in microvesicles prevents miRNA from degradation.^[36] Microvesicles (MV) are called spheroidal membrane blebs and it matures and

is released from a cell. MVs have important roles in cell to cell communication, cell differentiation, and tissue homeostasis. One important function of it is to transport miRNA without degradation and to provide bioavailability to miRNA.^[37] Bioavailable miRNA is mostly found in plants, human breast milk, bovine milk, and rice. When miRNA is taken up from a dietary source, first it is absorbed by the gastrointestinal tract. miRNA molecules perform their functions after they are transported to different tissues in the body. Plant-derived miRNAs are found to be stable during cooking and remain in the human body for more than an hour without a decrease in their concentrations. Interestingly, the absorption of miRNAs has been discovered to be selective. However, understanding dietary miRNA absorption and detecting exogenous miRNAs in mammals is still a work in progress.^[38]

miRNA FROM MILK

Both from humans and bovine, breast milk is already investigated widely for its potentiality of providing nutrients, microbiota, and biologically active compounds. Human breast milk includes miRNA and long non-coding RNA in its extracellular MVs. Studies show that miRNAs from mother's milk cause an enrichment in biological functions such as regulation of actin cytoskeleton, glycolysis, gluconeogenesis, aminoacyl-tRNA biosynthesis, and enrichment of the immunological pathways.^[39]

Human breast milk contains stable and highly expressed miRNAs and these include miR-148a-3p, miR-22-3p, miR-30d-5p, let-7b-5p, and miR-200a-3p all of which are related to significant functions.^[40]

Exosomes in milk are considered crucial signal packages for cell-to-cell communication between mother and infant. Milk-derived miRNAs in exosomes are identified in both whole milk and skimmed milk. Exosomal miRNAs from human breast milk are said to be resistant to harshness. Nonetheless, rigid lipid bilayer membranes of these exosomes prevent miRNA from degrading. miRNA is observed to be stable under acidic conditions of the gastrointestinal tract and even after pasteurization. Despite that, pasteurization and homogenization of milk cause the loss of some miRNAs. Statistics are showing that not all of it, but more than 60% of both miR-200c and miR-29b are degraded.^[41]

A study that compares exogenous miRNAs from sheep milk and cow milk suggests that despite the common miRNA exosomes in both mammals, sheep milk contains more human-like miRNAs.

Therefore, it is more suitable for human infants. The most expressed miRNA in the sheep milk is miR-148, which is a crucial regulator for B cell tolerance and therefore autoimmunity-related pathways.^[42]

Bovine milk also contains significant miRNAs that are complementary to human miRNAs, such as some miRNAs from miRNA-29 family.^[43] miRNAs from milk generally have important functions in consumers, such as in immune functions and cancer.^[44]

OTHER DIETARY SOURCES OF miRNA

According to recent studies, miRNA exosomes are found in many plants in addition to milk. Plant-derived miRNA exosomes are detected in rice, corn, moringa, arabidopsis thaliana, cabbage, spinach, lettuce, tomato and many more. miRNA exosomes in plants vary and each of them targets different organs in different organisms, mostly mammals, including mice and humans. Most of these dietary miRNAs share the same functions as endogenous miRNAs such as anti-cancer and anti-inflammatory effects.^[44]

Conclusion

This review attempted to integrate studies on the effect of natural compounds of miRNA and functions of dietary miRNAs. The functions of miRNAs, like those of other noncoding RNAs, are being thoroughly investigated. Even though many of its roles and how it is regulated are unknown, it is a growing field, similar to food science. The discovery of the relationship between food and miRNA regulation is promising for learning more about how miRNA can be modulated by natural compound intake. It has been demonstrated that miRNA regulation with polyphenols such as resveratrol, EGCG, curcumin, and quercetin has significant promising roles in pharmacology and treatment of various diseases. Furthermore, research on exogenous miRNA is a growing field of study. Nevertheless, there are many gaps about miRNA and nutrition in the literature as well as in nutriepigenomics. To understand it better and use it as an effective treatment, more research should be performed about how these mechanisms work and how bioavailable these molecules are.

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