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Review Article

Macronutrient modulation of mRNA and microRNA function in animals: A review

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ABSTRACT

Dietary macronutrients have been regarded as a basic source of energy and amino acids that are necessary for the maintenance of cellular homeostasis, metabolic programming as well as protein synthesis. Due to the emergence of "nutrigenomics", a unique discipline that combines nutritional and omics technologies to study the impacts of nutrition on genomics, it is increasingly evident that macronutrients also have a significant role in the gene expression regulation. Gene expression is a complex phenomenon controlled by several signaling pathways and could be influenced by a wide variety of environmental and physiological factors. Dietary macronutrients are the most important environmental factor influencing the expression of both genes and microRNAs (miRNA). miRNA are tiny molecules of 18 to 22 nucleotides long that regulate the expression of genes. Therefore, dietary macronutrients can influence the expression of genes in both direct and indirect manners. Recent advancements in the state-of-the-art technologies regarding molecular genetics, such as next-generation sequencing, quantitative PCR array, and microarray, allowed us to investigate the occurrence of genome-wide changes in the expression of genes in relation to augmented or reduced dietary macronutrient intake. The purpose of this review is to accumulate the current knowledge focusing on macronutrient mediated changes in the gene function. This review will discuss the impact of altered dietary carbohydrate, protein, and fat intake on the expression of coding genes and their functions. In addition, it will also summarize the regulation of miRNA, both cellular and extracellular miRNA, expression modulated by dietary macronutrients.

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1. Introduction

Epidemiological studies have shown that the life expectancy and the physiological conditions crucially depend on different macronutrients we take through various diets. The prime example is that the Greenland Eskimos have lower morbidity due to cardiovascular disease than the Eskimos who are living in Europe or in the US. This is primarily because of the dietary consumption of different nutrients. The Greenland Eskimo's food menu is dominated by fish and seafood whereas Eskimos in Europe and the US eat more meat and carbohydrate. Fish oil contains omega-3 fatty acid (20-carbon eicosapentaenoic acid) which has beneficial effects on maintaining the health of the heart. Although it is clear and well accepted that dietary consumption of macronutrients influences the pathophysiological status of an animal, the underlying molecular mechanisms are poorly understood. It is a general belief that a complex array of response elements regulates the expression of genes and these elements influence the transcription rate of a particular gene (Cousins, 1999). Dietary nutrients, especially macronutrients, can influence the rate of transcription of a given gene directly through interacting with the regulatory elements of the genome. Alternatively, macronutrients may act indirectly by affecting and/or modulating important signaling pathways (Sohel et al., 2018). However, it is often difficult to discriminate whether a nutrition–gene interaction as a result of a direct or indirect effect. Because of the involvement of several bioactive components, the indirect way of regulating the transcription of genes is a more

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complex process. For instance, dietary constituents of fiber can regulate the expression of genes indirectly through altering metabolites availability, mechanical stimuli, and hormonal signaling produced by the intestinal/colonic microflora. Short-chain fatty acids including butyric acid are produced by the colonic microflora as a consequence of water-soluble fiber metabolism. Butyric acid, in turn, can bind with the intracellular messenger G-protein to selectively regulate the expression of genes or directly interact with the regulatory sequence of DNA. The influence of macronutrients (carbohydrate, protein, and lipid) on gene and microRNA (miRNA) expression is discussed in the following sections.

2. Macronutrient mediated changes in the expression of genes

The diet has long been considered as a mixture of complex natural substances that provides both the energy and building blocks to develop and maintain an organism. The generally accepted notion is that food can regulate health by its nutritional constituents. Furthermore, consumption of dietary macronutrients enhances the release of a variety of hormones that can change gene function and powerfully affect signal transduction. The use of quantitative real-time PCR (qRT-PCR) gained the highest popularity to study dietary nutritional impacts on gene expression as it is a powerful tool to study the expression pattern of candidate genes in specific tissues of both humans and animals (Schwerin et al., 2002). As a result, understanding of the dietary influence on gene expression and molecular mechanisms started increasing. Later on, the GeneChip microarray system was employed to have a deeper understanding of underlying molecular mechanisms of dietary protein-induced alteration of the pathophysiological status of animals. The microarray is extremely effective and identifies multiple up- and down-regulated genes as a result of dietary manipulation at a single experiment which allows studying bioinformatics to identify critical pathways involved. Recently next-generation sequencing is used to identify the association between nutrition and genetics as this platform generates millions of sequences in a high-throughput and cost-effective manner.

2.1. Carbohydrate regulation of gene expression

Dietary carbohydrate has a strong influence on the expression of a number of genes related to metabolic pathways predominantly those are involved in carbohydrate metabolism including glycolysis/gluconeogenesis, fructose and mannose metabolism, pentose phosphate pathway, inositol metabolism, aminosugar metabolism, and galactose metabolism (Wang et al., 2009). It is important to note that the quantity of dietary carbohydrate also has dramatic effects on the expression of several genes associated with cell adhesion, cell cycle and growth control (Wang et al., 2009; Zhou et al., 2015). The research conducted by Kallio et al. (2007) demonstrated the possibility of changes in the expression of a panel of genes in individuals consuming diets that have effects on postprandial insulin concentrations. The authors assigned adults to rye-pasta (low insulin response diet) and oat-potato-wheat (high insulin response diet) for 12 wk. Gene expression in subcutaneous fat was examined at baseline and at 12 wk using microarrays and qRT-PCR platforms. In the low-insulin-response group, 71 genes were found to have decreased expression. In addition, bioinformatics analysis revealed several of these down-regulated genes have links to apoptosis and insulin-signaling pathways. By contrast, in the high-insulin-response group, 62 genes linked to immunity, stress, and interleukin pathway were found to have increased expression and none showed decreased expression (Kallio et al., 2007). Interestingly, the modifications of gene expression profile in the subcutaneous adipose tissue through carbohydrates are not linked with body weight gain or loss.

After digestion, most dietary carbohydrates turned into glucose in the small intestine and subsequently transported into the bloodstream. This glucose is the primary fuel for skeletal muscles, the brain and other organs to perform their functions properly. Previous research has demonstrated that exposure to a high level of glucose induces proliferation and differentiation in mesenchymal stem cells (Li et al., 2007) and vascular smooth muscle cells (Yamamoto et al., 2000) in vitro. In addition, a high level of sucrose in the diet may result in the proliferation of intestinal epithelial cells and tumorigenesis by increasing the level of hepatic insulin like growth factor-1 (*IGF-1*) mRNA in APC^{Min} mice in vivo (Wang et al., 2009). Furthermore, high dietary sucrose significantly altered mRNA expression of 109 known genes in the small intestinal epithelium including many involved in several metabolic pathways compared to cornstarch-containing diet (Wang et al., 2009). One of the significantly affected metabolic pathways is transcription and translation regulation where pleckstrin homology, Sec7 and coiled-coil domains 3 (*PSCD3*), *SMAD3*, PR domain zinc finger protein 2 (*PRDM2*) genes are significantly upregulated in the high starch group (Wang et al., 2009). Despite their important function in making proteins, these genes are known to have a significant role in different diseases including retinal cancer and Loeys-Dietz syndrome type III. It is important to note that consumption of higher dietary sucrose (60%) does not cause a dramatic increase in body weight in obese rat or induce obesity in lean rats. Interestingly, high-sucrose feeding regimen for one week induced the enhanced expression of genes of heat shock proteins (HSP27 and HSP70) and suppressed the production of nitrate and nitrite (NOx) in the rat brain, whereas the standard diet did not show such effects (Kanazawa et al., 2003). It is clear that the high-sucrose diet has no effects on body weight gain in the obese or lean rat, however, it has favorable effects on the brain through modulation of the expression of genes related to stress.

It has been shown that the level of dietary carbohydrates has immense impacts on the growth, antioxidant capacity, pathogen resistance, and immune response in the juvenile Black carp fish (Wu et al., 2016). A low or high level of dietary carbohydrate resulted in growth abnormalities. Gene expression analysis revealed that the optimum level of carbohydrate (288.4 g/kg) significantly increases the expression of antioxidant genes including glutathione peroxidase (*Gpx*), catalase (*CAT*), and superoxide dismutase (*SOD*) and subsequently resulted in higher total antioxidant capacities (TAOC) in the liver. In addition to antioxidant activities, the expression levels of immune-related genes including interferon (*IFN*) and tumor necrosis factor-α (*TNF-*α) in the liver and blood samples of juvenile Black carp *Mylopharyngodon piceus* also increases in comparison to the low or high carbohydrate diets (Wu et al., 2016). An appropriate level of carbohydrate may boost the antioxidative capacity and immune response in carp fish which may subsequently enhance the pathogen resistance and finally increase the growth. Similar results were observed in juvenile shrimps (Ding et al., 2017) where the authors emphasize that the lower level of dietary carbohydrates resulted in a reduction of growth performance.

Heat stress is a major problem that causes suboptimal production performance in domestic animals. Heat stress drastically down-regulates the function of mitochondria (White et al., 2012), while manipulation of exogenous carbohydrate supplementation during exercise may induce stimulation of mitochondrial biogenesis through alteration of the expression of metabolic genes in human skeletal muscle (Margolis and Pasiakos, 2013). By manipulating carbohydrate supplementation, Dumke et al. (2013) demonstrated the influence of exercise on skeletal muscle

metabolic activity in response to heat. The authors showed that carbohydrate ingestion during exercise represses the expression of ncoupling protein 3 (*UCP3*) mRNA, which transfers the anions from the inner to the outer mitochondrial membrane, however, had no effect on the expression of mitofusin 2 (*MFN2*), glucose transporter type 4 (*GLUT4*), and peroxisome proliferator-activated receptor-γ coactivator (*PGC*)-*1α*.

Acute starvation and refeeding are a worldwide health issue nowadays. In the past few decades, a considerable number of studies highlighted the relationship between unhealthy eating behaviors such as picky eating, overeating, skipping meals and the increased risk of atherosclerosis, type 2 diabetes, cardiovascular and liver diseases (Yasutake et al., 2014). Irregular eating habits mostly ended up with the ingestion of high carbohydrate-high-fat fast food causing several food-associated health problems. Even refeeding with a standard diet after long starvation can induce the expression of genes associated with inflammation in the liver which may be mediated by Toll-like receptor 2 (*Tlr2*) in mice where dietary carbohydrate plays a crucial role (Oarada et al., 2013). Findings of these studies are summarized in Table 1.

2.2. Protein regulation of gene function

Protein is an essential macronutrient required by humans and animals for their proper growth and development. Malnutrition caused by an insufficient supply of protein may affect the physiologic and pathologic status of an organism. Hydrolysis of proteins by boiling yields a bunch of small molecules known as amino acids. Depending on the animal's ability to synthesize, these amino acids are classified as nutritionally essential amino acid (EAA) and nonessential amino acids (NEAA). Overfeeding or restriction of dietary protein may cause severe health consequences through altering the expression of genes that are central to several pathways. Dietary proteins mediate the majority of the pleiotropic effects through changes in the expression of involved target genes. Several genes have been found to be influenced through dietary protein in humans as well as different experimental and domestic animals (Hesketh et al., 1998; Starr et al., 2015). For instance, the IGF-1 system and the involved genes are extremely sensitive to the dietary protein inputs (Wan et al., 2017). Any expression deviation of these genes may cause metabolic abnormalities and growth restriction. One of the earliest studies investigating the influence of dietary proteins on the expression of genes revealed that the activity of plasma renin differs depending on the level of dietary input of proteins, being higher on a high protein diet. Compared to the standard 20% protein diet, 50% high protein diet elevated the expression of renal renin mRNA while 6% low protein diet lowered the expression (Rosenberg et al., 1990). Using GeneChip microarray Endo et al. examined for the first time the consequence of dietary protein intake on the expression of hepatic genes and subsequently, demonstrated that the expression of several genes was affected by different protein diets (Endo et al., 2002).

2.2.1. Quantity of protein

High protein diets are generally promoted by some nutritional supplement industry because of their important role in muscle growth and development. Furthermore, high dietary proteins are widely used to control obesity and overweight as it has been shown that high protein diets reduce the mRNA abundance of lipogenic genes (fatty acid synthase [*FASN*], acetyl-CoA carboxylase alpha [*ACACA*], and acetyl-CoA carboxylase beta [*ACACB*], etc.) in the liver (Chaumontet et al., 2015) which inhibits lipogenesis and reduces obesity. However, several studies have demonstrated that overfeeding of protein or overuse of protein supplements could cause several diseases including cancer or cardiovascular diseases and other disorders (Norat and Riboli, 2001; Pedersen et al., 2013). Experiments on both humans (Hannan et al., 2000) and laboratory animals (Amanzadeh et al., 2003) demonstrated that high dietary protein can create increased acid load in body fluids which is buffered by bone calcium resulting in excessive calcium loss. However, studies have shown that protein could be beneficial for bone health under some dietary conditions such as adequate calcium supplementation (Mangano et al., 2014). Although a combination of high proteins and low carbohydrates may help to control obesity in the short term, it can lead to the formation of kidney stones under circumstances like low fluid intake. Diets rich in protein strongly affect the expression of hepatic genes including amino acid transport and catabolism and prevent fatty liver disease by enhancing lipid secretion into very low density lipoprotein (VLDL) particles (Schwarz et al., 2012).

On the other hand, protein deficiency has also been found to have negative consequences on the growth and development of humans, livestock and other laboratory animals (Christian and Stewart, 2010; Rehfeldt et al., 2011). When mammals are exposed to low protein diet or diet missing some EAA, the plasma concentrations of certain amino acid dropped dramatically, which may cause aberrant expression of different growth related genes. For instance, low dietary protein intake resulted in a lower abundance of genes involved in endopeptidase activity and cell motility, which are critical to the invasion of trophoblast in the early pregnancy

Table 1
Detailed information of the selected experiments focusing on carbohydrate mediated changes in gene expression.

Macro-nutrient	Feeding cohort	Organism, tissue/organ	Platform	DE genes	Important genes	References
Carbohydrate	sucrose vs. cornstarch	mice, small intestine and colon epithelial cells	microarray	58 ↑ 37 ↓	*IGF-1*, *IGF-2*, *IGFBP3*, *Pcna*, *Pik3c2a*, *Aldrl6*, *Scd2*, *Timm23*, *Smad3*, *Rasa3*, *PSCD3*	Wang et al. (2009)
Carbohydrate	rye-pasta vs. oat-potato-wheat	humans, adipose tissue	microarray	62 ↑ 71 ↓	*IGFBP5*, *LIPE*, *DUSP6*, *MKNK2*, *GAS7*, *CCND2*, *SKG*, *SLC40A1*, *FTHP1*, *TCF7L2*, *CD34*, *INSR*, *PPP1R12B*, *MRPS30*	Kallio et al. (2007)
Carbohydrate	high sucrose	rats, brain	qPCR assay	–	*HSP27*, *HSP70*	Kanazawa et al. (2003)
Carbohydrate	dextrin, graded level (0 to 500 g/kg)	juvenile black carp, liver tissue	qPCR assay	–	*HEPC*, *TNF-α*, *IFN-α*, *LYZ*, *NRAMP*, *C3*	Wu et al. (2016)
Carbohydrate	cornstarch, graded level (50 to 300 g/kg)	juvenile prawns, muscle	qPCR assay	–	*HK*, *PK*, *PYC*, *G6Pase*	Ding et al. (2017)
Carbohydrate	malto-dextrin	humans, muscle	qPCR assay	–	*MFN2*, *GLUT4*, *PGC-1α*, *UCP3*	Dumke et al. (2013)
Carbohydrate	sucrose, cornstarch	mice, liver	qPCR assay	–	*Glut2*, *Tlr2*, *Tlr4*, *Hspd1*, *Hmgb1*, *Grp94*	Oarada et al. (2013)

DE = differentially regulated; ↑ = upregulated; ↓ = downregulated; qPCR = quantitative PCR.

(Ren et al., 2012). Restriction of 50% protein in the diet of mice during pregnancy from d 10.5 to 17.5 typically upregulates several genes involved in epigenetic regulators, negative regulation of cell growth and apoptosis (Gheorghe et al., 2009). Besides detrimental effects on maternal health, protein restriction during pregnancy plays a critical role in the suboptimal growth and development of offspring by altering the folliculogenic and steroidogenic genes and their regulatory miRNA (Sui et al., 2014). In addition, protein restriction influenced fetal growth by regulating the expression mRNA abundance of placental growth related genes (Starr et al., 2015). It has recently been reported that a high or low protein diet alters the expression of several key genes in the fetal skeletal muscle of sheep that could affect growth and development (Cinar et al., 2018). The level of protein is also crucial for the postnatal muscle development of growing animals. Very low protein intake severely downregulates the abundance of amino acid transporter mRNA including proton-assisted amino acid transceptors 2, L-type amino acid transceptor 1, and sodium-coupled neutral amino acid transceptor 2 in the muscles of growing pigs (Li et al., 2017). The lower abundance of amino acid transporter mRNA in the muscles resulted in inadequate absorption of EAA to the growing muscles it requires and finally, restricts the growth. Interestingly, when a low level of protein (3% lower than the recommended) was fed to growing pigs, it resulted in a significantly higher level of these amino acid transporter genes in the muscles (Li et al., 2017). It is highly likely that slightly lower protein intake probably enhances the abundance of amino acid transporter mRNA to efficiently absorb the EAA in the muscles of growing pigs.

2.2.2. Origin of protein

In addition to the quantity of dietary protein, the source of protein (whether from animal or plant) may play a role in the growth and a variety of metabolic pathways. In a comprehensive study, Song and colleagues investigated the effects of recommended levels of soy and meat proteins on the expression of hepatic transcriptomics as well as the physiological markers of the metabolic syndrome (Song et al., 2016). Semi-synthetic diets for both soy and meat source were fed to male rats for one week and casein was used as a reference protein. Interestingly, the results revealed that the growth was significantly reduced in the soy protein regimen while the meat protein regimen showed no difference in comparison to those of the casein-fed control group. A total of 1,571 and 1,369 genes were found to be differentially regulated in the liver by soy and meat protein, respectively. Many signaling pathways including insulin signaling, lipid, energy, and amino acid metabolic pathways were affected by the differentially regulated genes (Song et al., 2016). Similar results were reported for juvenile rainbow trout (*Oncorhynchus mykiss*) when they were fed either soy protein or fishmeal (Wacyk et al., 2012). The authors demonstrated that plant-based dietary protein sources are less efficient in terms of protein retention efficiency and growth performance. The source of protein has a significant effect on the expression of several hepatic genes as well (Wacyk et al., 2012). The distinct physiological and gene expression changes in experimental animals through soy and meat/fish protein source provides a deeper understanding of the importance of the source of proteins in domestic animals as well as humans. Dietary protein-induced changes in the expression of genes are listed in Table 2.

2.3. Dietary lipid-mediated alteration of gene expression

Dietary fat is another macronutrient which serves a number of essential functions. However, high dietary fat is considered an important environmental risk factor that is associated with obesity and other metabolic disorders such as stroke, coronary heart disease, hypertension, and type 2 diabetes mellitus. Although there is a complex relationship between metabolic syndrome and dietary input of fat which includes several genes and genetic interactions, the results of different research provide clues to complete the complex puzzle of dietary fat induced complications. Higher intake of dietary fat induces rapid weight gain and adiposity not only in laboratory animals but also in humans. When dietary energy intake, in terms of fat, chronically exceeds expenditure may lead to a variety of obesity-related disorders.

2.3.1. Effects of the quantity of fat in the diet

A variety of complications including hyperinsulinemia, hypertriglyceridemia, hyperglycemia, and higher low-density lipoprotein (LDL) are often associated with diets with higher fat. Diets high in fat can also have adverse impacts on insulin-responsive tissues. It is specifically true for the adipose tissues where lipid homeostasis takes place and which secretes bioactive lipids and adipokines to regulate the balance of systemic energy (Almon et al., 2015). G-protein-coupled receptor (GPR)109A and GPR81 are G protein-coupled cell surface receptors that mediate antilipolytic effects and located predominantly on adipocytes. Any metabolic changes in the environment can be sensed by the adipocytes through these receptors and responded through lipolytic regulation and release of products including pro or anti-inflammatory adipokines and free fatty acids. The level of dietary fat can regulate the expression of these genes in adipose tissue. When male C57BL/6 mice were fed a high-fat diet for 11 wk, the expression *GPR109A* and *GPR81* genes were significantly downregulated in the adipose tissue of epididymal fat pads (Wanders et al., 2012). In addition, the decrease in the expression of *GPR81* and *GPR109A* genes is positively correlated with the expression of the peroxisome proliferator-activated receptor gamma (*PPARγ*) gene, a regulator of glucose metabolism and fatty acid storage, in adipose tissue (Wanders et al., 2012). It is expected that low dietary fat will enhance the expression of the *PPARγ* gene in adipose tissues. However, the expression of the *PPARγ* gene in response to a low-fat diet is partly true in the case of growing calves. Low-fat diet resulted in an increase of the expression of *PPARγ* gene at 0 to 112 d of age of growing calves, whereas it is decreased at 112 to 224 d of age in response to low dietary fat (Segers et al., 2017). In another study, Anunciado-Koza and colleagues showed that the expression of an array of genes including Secreted frizzled-related protein 5 (*Sfrp5*), bone morphogenetic protein 3 (*Bmp3*), mesoderm specific transcript (*Mest*), and WNT Signaling Pathway Inhibitor 1 (*Nkd1*) was significantly upregulated in the adipose tissues of mice fed a high-fat diet in comparison to that of basal low-fat diet-fed mice (Anunciado-Koza et al., 2015). Importantly, these genes are known as predictive indicators of the susceptibility to the development of obesity in the future. The effects of low dietary fat on the global expression of genes revealed that very few transcriptional changes in the liver of the animals of same-sex and strains. However, considerable variability was observed in the transcriptome profile of mice of the same strain and sex when they were fed a high-fat diet (Shockley et al., 2009). Furthermore, functional annotation and pathway analysis identified a number of pathways including cholesterol biosynthesis, liver damage, and immune response were affected by the differentially regulated genes due to a varying dietary fat input (Shockley et al., 2009). Offspring from high-fat diet-fed mothers were significantly heavier at weaning with impaired insulin sensitivity which is associated with increased plasma

Table 2
Information of selected studies that investigated the role of dietary protein on the expression of genes.

Macro-nutrient	Feeding cohort	Organism, tissue/organ	Platform	DE genes	Important genes	References
Protein	commercial diet, 24% vs. 6% protein	mice, placenta	microarray	214 ↑ 109 ↓	*Cxcl12*, *Gja1*, *Plau*, *Gm4787*, *Htra1*, *Plau*, *Prss23*, *Creb3l1*, *Etv5*, *Foxp4*, *Gata1*, *Gata3*, *d79a*, *Fas*, *Crb3*, *Hoxa13*, *Shank3*	Starr et al. (2015)
Protein	soybean, 14% and 20% curd protein	swine, liver	next generation sequencing	667 ↑ 652 ↓	*CMBL*, *PPIF*, *NDUFA11*, *MMACHC*, *AP2S1*, *PARVB*, *CHCHD5*, *CHCHD5*, *ATP5J2*, *CD63*, *ATPAF2*, *PPP1R1A*	Wan et al. (2017)
Protein	casein vs. protein free diet	Wistar rats, liver	microarray	97 ↑ 184 ↓	*Igfbp2*, *Igf1*, *Phgdh*, *Tbg*	Endo et al. (2002)
Protein	high protein vs. standard protein	Wistar rats, liver	microarray	–	Gls2, *Sds*, *Prodh*, *Mccc2*, *Pck1*, *G6pc*, *Gpam*, *Agpat1*, *Acls3*, *Crat*, *Cpt1a*, *Cpt1b*, *Acat1*	Chaumontet et al. (2015)
Protein	commercial diet, high vs. normal protein	mice, liver	microarray	–	*Acmsd*, *Ppargc1a*, *Got1*, *Mthfd1l*, *Idh2*, *Cox7a1*, *Gnpda1*, *Acsl4*, *Gpx6*, *Cyp2b10*, *Nnmt*, *Gstm3*, *Gsta2*, *Inhba*, *Klf10*, *Egr1*, *Bcl6*, *Id2*	Schwarz et al. (2012)
Protein	low vs. standard protein	mice, placenta	microarray	91 ↑ 153 ↓	*Dhcr24*, *Bcl2*, *Fastk*, *Fntb*, *Cdh5*, *Inpp5d*, *Ncor2*, *Hdac7*, *Rai17*, *Hipk2*	Gheorghe et al. (2009)
Protein	low vs. standard protein	swine, ovary	qPCR	–	*BAX*, *Bcl-2*, *BMP15*, *BMP4*, *PCNA*, *3βHSD1*, *17βHSD2*, *CYP19A1*, *CYP17A1*, *StAR*, *FSHR*, *LHR*, *ERα*	Sui et al. (2014)
Protein	corn-soy bean, standard, low and very low protein	swine, skeletal muscle	qPCR	–	*SNAT2*, *LAT1*, *PAT1*, *PAT2*	Li et al. (2017)
Protein	soy vs. meat protein	rats, liver	next generation sequencing	297 ↑ 279 ↓	*Slc16a5*, *Slc7a11*, *Asns*, *Gsta5*, *Phgdh*, *Fut1*, *Csmd1*, *Igfbp2*, *Mt2A*, *Chac1*, *Prkcdbp*, *Arhgap22*	Song et al. (2016)

DE = differentially regulated; ↑ = upregulated; ↓ = downregulated; qPCR = quantitative PCR.

concentration of interleukin (IL)-1β and TNF-α and the increased expression of taste receptor type 1 member 1 (*Tas1R1*), *IL-1β*, *TNF-α*, and nucleotide-binding domain and leucine-rich repeat containing protein 3 (*NLRP3*) genes in the gut (Reynolds et al., 2015). Expression of metabolic genes such as glucokinase (*Gck*), *FASN*, and *PPARα* was significantly elevated in the liver of offspring in response to high-fat diet in parents, indicating there is a progressing insulin resistance through transgenerational effects (Park et al., 2015).

2.3.2. Dietary fat-induced regulation of genes related to oxidative stress

Dietary fat intake markedly influences the abundance of the mRNA genes crucial for the oxidative metabolism and transportation of fatty acid in the skeletal muscles. Consumption of high dietary fat for a short time may result in a selective increase in the expression of fatty acid translocase (*FAT*)/*CD36* and *BHAD* genes in the skeletal muscles of humans. Gene abundance due to fatty acid-mediated interactions could be a significant component in skeletal muscle adaptive activity (Cameron-Smith et al., 2003). Furthermore, it has been shown that high-fat diet in insulin-sensitive mice and humans were involved in the changing the expression of genes associated with decreased abundance of mitochondrial protein-encoding nuclear genes (e.g., mitochondrial carrier proteins), decreased expression of genes involved in oxidative capacity (e.g., electron transport chain associated genes), and mitochondrial biogenesis-related genes (e.g., *PGC-1α* and *PGC-1β*) (Mizunoya et al., 2013). Insulin resistance and hyperlipidemia often caused by a high-fat diet which subsequently has negative impacts on kidney and liver function. Feeding a high-fat diet can also increase the inflammation as well as oxidative stress by modulating the expression of hepatic genes. A study conducted by Okere et al. reported that on low-fat diet, hypertensive animals could exhibit higher expression of myosin heavy chain switching (2α to β), atrial natriuretic factor mRNA, and decreased the activity of medium-chain acyl-coenzyme A dehydrogenase and citrate synthase. All of these conditions can be reversed by feeding a high-fat diet (Okere et al., 2006). From these results, it can be concluded that increased dietary lipid intake can alter the expression of genes in response to hypertension, left ventricular remodeling, reduce cardiac growth, and contractile dysfunction. Changes in the expression of genes due to dietary fat are presented in Table 3.

3. Macronutrients can influence miRNA expression and function

3.1. Macronutrients and cellular miRNA

miRNA are a class of small non-coding RNA of approximately 22 nucleotides in length that principally regulate gene expression either by mRNA destabilization or translational repression (Tesfaye et al., 2017). miRNA are estimated to comprise 1% to 5% of animal genes and thought to regulate at least approximately 60% of genes that are involved in all cellular processes. In addition, to identify active regulatory miRNA in various tissues, several studies have shown the relevance of miRNA with numerous pathological, fertility and developmental processes (Hossain et al., 2012) and most recently nutrition (García-Segura et al., 2013). The growing number of research in the field of nutritional impact on miRNA expression and function indicates the interest and importance to understand the dynamic relationship of nutrition and miRNA.

3.1.1. Dietary protein intake and regulation of miRNA function

The function and expression of miRNA in a given microenvironment have been shown to be dramatically dysregulated by the environmental alteration, i.e. oxidative stress (Sohel et al., 2019). Therefore, it is highly likely that the expression and function of certain miRNA can also be modulated by nutrition, macronutrients in particular, either via deficiencies or augmented intake. For instance, deprivation of macronutrients modulates the expression of 30 miRNA in the mammary gland in lactating goat, where 14 miRNA are up-regulated and 16 miRNA are down-regulated (Mobuchon et al., 2015). It is important to note that both the

Table 3
Dietary fat induced changes in the expression of genes.

Macro-nutrient	Feeding cohort	Organism, tissue/organ	Platform	DE genes	Important genes	References
Fat	standard vs. high fat	mice, white adipose tissue	qPCR	–	*Gpr109a*, *Gpr81*	Wanders et al. (2012)
Fat	high vs. low fat	cattle, muscle	qPCR	–	*ACLY*, *ADIPOQ*, *ADIPOR2*, *CEBPA*, *DGAT2*, *FABP4*, *FASN*, *INSIG1*, *LEP*, *MTG1*, *PCK1*, *PPARG*, *RPS15A*, *SCD*, *SREBF1*	Segers et al. (2017)
Fat	commercial diet, standard vs. high fat	mice, epididymal fat	qPCR	–	*Mest*, *Sfrp5*, *Bmp3*, *Nkd1*	Anunciado-Koza et al. (2015)
Fat	dairy fat, high vs. standard fat	mice, liver	microarray	2,527 ↑ 2,085 ↓	*Copg*, *Atp6v0d1*, *Golga7*, *Psph*, *Trappc4*, *Dpm2*, *Psmb5*, *Dhrs1*, *Ppm1a*, *Psenen*, *Anapc1*, *Mrpl43*, *Xpo7*, *Nmt1*	Shockley et al. (2009)
Fat	standard vs. high fat	rats, upper gut samples	qPCR	–	*Tas1R1*, *Tas1R3*, *IL-1β*, *TNFα*, *NLRP3*, *IL-10*, *PYY*, *Ghrelin*	Reynolds et al. (2015)
Fat	soybean vs. fish oil	Wistar rats, muscle	qPCR	–	*MyHC1*, *MyHC2A*, *MyHC2X*, *MyHC2B*, *LPL*, *UCP3*, *PDK4*, *MTCO2*, *PPARδ*, *PGC1α*, *FOXO1*, *MyoD*	Mizunoya et al. (2013)
Fat	high vs. low fat	rats, hearts	qPCR	–	*MHC-β*, *ANF*	Okere et al. (2006)

DE = differentially regulated; ↑ = upregulated; ↓ = downregulated; qPCR = quantitative PCR.

exercise and EAA intake modulate the expression of muscle-specific miRNA, commonly known as myomirs, including miR-499, miR-206, miR-133a/b, and miR-1 (Pasiakos and McClung, 2013). Characterization of these 30 nutriregulated miRNA might provide us a clear understanding of gene regulation in response to nutrition in ruminants.

Maternal low protein diets found to have significant impacts on the expression of folliculogenic and steroidogenic genes and their regulatory miRNA in the ovaries of neonatal piglets suggesting a potential role of maternal low protein diet on ovarian development and function through modulating the expression of key miRNA (Sui et al., 2014). A diet lack of amino acids can result in a change in the expression of several miRNA. When a methionine-choline-deficient diet was fed, the animals showed liver steatosis, liver injury, and nonalcoholic fatty liver. Interestingly, under such conditions, the expression of miR-182, -183, -199a, -705, and -1224 was upregulated in the liver indicating the association of miRNA with diet induced metabolic disorders (Dolganiuc et al., 2009). Maternal dietary protein can affect lipid metabolism in offspring which may mediate by miRNA. Ccaat-enhancer-binding Protein beta (C/EBPβ) and PPARγ are well-established transcription factors involved in lipid metabolism during adipogenesis and a master regulator of adipocyte differentiation and insulin sensitivity. PPARγ and C/EBPβ are predicted to be a potential target of miR-130b and miR-374b, respectively. The body weight and backfat thickness of offspring were significantly decreased in the low protein group which is characterized by significant down regulation of the expression of *PPARγ* and *C/EBPβ* genes along with a significant increase of miR-130b and miR-374b (Pan et al., 2013). Dietary macronutrient-induced changes in the cellular miRNA function are presented in Table 4.

3.1.2. Carbohydrate regulation of miRNA function

The availability or shortage of carbohydrates also can modulate the expression of miRNA. Glucose depletion-induced oxidative stress has been shown to enhance the acetylation of the miR-466h-5p promoter region, which led to increasing the expression of miR-466h-5p (Druz et al., 2012). Lethal (let)-7 miRNA is one of the most studied miRNA family specifically targets genes that are associated with type 2 diabetes and is implicated in the regulation of peripheral glucose metabolism. It has been shown that the promoter activity and let-7 miRNA expression is dynamically regulated in response to glucose, TNF-α, and caffeine (Katayama et al., 2015).

Phosphatase and tensin homolog *(PTEN)*, a tumor suppressor gene and activator of Akt kinase and induces glomerular mesangial cell hypertrophy in diabetic nephropathy, has been found to be a potential target of miR-26a. High glucose diet increased the expression of miR-26a which reduced the PTEN protein expression and resulting in mesangial cell hypertrophy (Dey et al., 2015). In addition, hyperglycemia also resulted in an increased expression of miR-21 as well as in a decreased expression of its target PTEN in mouse and lead to renal cell hypertrophy which is a characteristic of diabetic nephropathy (Dey et al., 2011). In contrast to mammalian, hyperglucidic feed did not affect the expression of metabolism related miRNA in juvenile rainbow trout (Geurden et al., 2014).

3.1.3. Fat-induced changes in miRNA function

High-fat diets are believed to contribute to the global epidemic of several metabolic disorders such as obesity, cardiovascular disease, and probably cancer. A number of recent studies have demonstrated the putative role and changes in the expression of miRNA related to the pathogenesis of diseases that are associated with high-fat diets. For instance, it has been shown that maternal high-fat diet during pregnancy and lactation significantly reduced the expression levels of let-7a, let-7b, let-7c, miR-26a, miR-122, miR-192, miR-194, miR-483*, miR-494, and miR-709, while the hepatic expression of *IGF-2* and *PPARα* were markedly increased (Zhang et al., 2009). In addition, maternal high-fat diet results in a significantly different expression of 10 miRNA in the germ cells of F1 male offspring and 25 miRNA in the mammary glands of F3 females (Nguyen et al., 2014). It is interesting to note that 4 miRNA were down-regulated in both F1 male germ cells and F3 mammary glands which have been linked to increased susceptibility to many cancers, including breast cancer (Nguyen et al., 2014) suggesting that maternal dietary exposures during pregnancy can initiate epigenetic inheritance of increased risk of breast cancer through changes in miRNA. HMG-box transcription factor 1 (*Hbp1*) is a target of miR-21 and is a transcriptional activator of *p53* which is commonly known as a tumor suppressor and an inhibitor of lipogenesis. High-fat diet induced the higher expression of miR-21 and subsequently suppress the expression of *Hbp1* and *p53* which is associated with the lipid accumulation in the liver and cancer progression (Wu et al., 2015).

Calorie restriction (CR) generally means a reduction of dietary intake than ad libitum levels without malnutrition. Both CR and low-fat diet have a profound impact on miRNA expression which is associated with several physiological alterations. For example, CR significantly down-regulates the expression of miR-140-3p and subsequently enhanced the expression of a SIRT1 protein which is a potential target of miR-140-3p (Pando et al., 2012). Sirtuin 1 (*SIRT1*) gene found in the mammalian cell that helps to promote survival

Table 4
Dietary macronutrient induced changes in the expression of cellular microRNA (miRNA).

Macro-nutrient	Feeding cohort	Organism, tissue/organ	Platform	DE miRNA	Top miRNA	References
Carbohydrate, protein, fat	ad libitum vs. food deprived	goats, mammary gland tissue	next generation sequencing	14 ↑ 16 ↓	miR-126-3p, miR-6119-5p, let-7c-5p, miR-99a-5p, miR-125b-3p, miR-140-3p, miR-409-3p, miR-451-5p, miR-660-5p, miR-99a-3p, miR-188-5p, miR-196a-5p, miR-204-5p, miR-222-3p, miR-223-3p, miR-494-3p	Mobuchon et al. (2015)
Protein	low vs. standard protein	swine, ovary	qPCR	–	miR-378, miR-98, miR -let-7d-5p, miR-140-5p, miR-140-3p, miR-let-7c, miR-423-5p, miR-423-3p, miR-17-5p, miR-421-5p	Sui et al. (2014)
Protein	standard vs. methionine choline deficient	mice, liver	microarray	–	miR-27b, miR-214, miR-199a-3p, miR-182, miR-183, miR-200a, and miR-322, miR-182, miR-183, miR-199a-3p, miR-705	Dolganiuc et al. (2009)
Protein	standard vs. low protein	swine, adipose tissue	qPCR	–	miR-130b, miR-374b	Pan et al. (2013)
Carbohydrate	glucose deprivation	mouse cell lines	qPCR	–	miR-466h-5p	Druz et al. (2012)
Carbohydrate	high glucose	rat glomerular mesangial cells	qPCR	–	miR-26a	Dey et al. (2015)
Carbohydrate	high glucose	kidney glomerular mesangial cells	qPCR	–	miR-21	Dey et al. (2011)
Carbohydrate	glucose and gelatinized starch, high vs. low	rainbow trout, liver and midgut	qPCR	–	miR-29, miR-107, miR-33, miR-143	Geurden et al. (2014)
Fat	standard vs. high fat	mice, liver	microarray	10 ↑ 23 ↓	miR-503*, miR-379, miR-770-3p, miR-369-3p, miR-197, miR-21*, miR-328, miR-471, miR-207, miR-667	Zhang et al. (2009)
Fat	standard vs. high fat	mice, liver	qPCR	–	miR-21	Wu et al. (2015)
Fat	standard vs. low	rats, epiphyseal growth plate	qPCR	–	miR-140-3p	Pando et al. (2012)
Fat	standard vs. caloric restriction	mice, heart tissue	qPCR array	18 ↑ 24 ↓	miR-21, miR-92a, miR-27, miR-29, miR-208, miR-214	Noyan et al. (2015)
Fat	ad libitum vs. caloric restriction	mice, colon mucosa	qPCR	–	miR-16, let-7f, miR-351, miR-150, miR-425, miR-196a, miR-138, miR-155	Olivo-Marston et al. (2014)

DE = differentially regulated; ↑ = upregulated; ↓ = downregulated; qPCR = quantitative PCR.

during energy scarcity and its abundance increased in a tissue-specific manner in response to calorie restriction. Short-term CR has been found to be involved in the changes of mRNA and miRNA profiles associated with the circadian clock, oxidative stress, immune function, apoptosis, metabolism, angiogenesis, cytoskeleton and extracellular matrix (Noyan et al., 2015). Furthermore, short-term CR is also associated with improved cardiac function compared to long-term CR through the reduced abundance of caspase 3 and activation of pro-survival signaling pathways (Noyan et al., 2015).

Moderate CR without malnutrition is recognized to have an anti-aging effect and extend lifespan in many organisms. Expression and activity of miR-144 were significantly increased in aged cells, while CR results in a decrease in expression of miR-144 (Csiszar et al., 2014). Expression and transcriptional activity of Nrf2 both were found to be significantly reduced in aged cells, whereas CR prevents Nrf2 dysfunction through significant down-regulation of miR-144. Furthermore, CR reduced age-related impairment of angiogenic processes, including cell proliferation, adhesion to collagen, and inhibits apoptosis in cerebromicrovascular endothelial cells. Characterization of CR-induced changes in the expression of miRNA suggests that they may affect several critical functions and pathways in endothelial cell homeostasis (Csiszar et al., 2014). High-fat diet induced obesity is another epidemic risk factor that is associated with the aging process and colon cancer, while the CR diet regimen decreases the risk of colon cancer. CR significantly decreased cytokines and IGF-1 expression along with differential expression of several miRNA including let-7, mir-16, mir-425, mir-196, mir-150, mir-155, mir-351, mir34, and mir-138. Clearly suppressive effects of CR on colon cancer are associated with alterations of several biological pathways and miRNA (Olivo-Marston et al., 2014).

3.2. Macronutrients and extracellular miRNA function

While the majority of miRNA are detected intracellularly, a handful of miRNA, commonly known as circulating miRNA or extracellular miRNA (ECmiRNA), have also been detected outside cells, mainly in various bio-fluids (Sohel, 2018). ECmiRNA are found in follicular fluid (Sohel et al., 2013, 2014), blood plasma (Noferesti et al., 2015), milk (Sun et al., 2015), amniotic fluid (Sun et al., 2016), and several other bodily fluids (Weber et al., 2010) and cell culture media (Valadi et al., 2007). Moreover, the expression profile of extracellular miRNA from different types of body fluids in relation to different physiological/pathological conditions showed a specific pattern indicating that ECmiRNA are selectively released from the cells (Sohel, 2016). ECmiRNA can be released to the extracellular environment through a variety of pathways including exosomes, microvesicles, and protein-mediated pathways. For a detailed review of ECmiRNA release, please see (Sohel, 2020). Both pathological conditions and environmental factors can influence the ECmiRNA expression in body fluids. Therefore, it is highly likely that the expression of ECmiRNA could also be dysregulated by the dietary intake of macronutrients.

3.2.1. Dietary fat-induced changes in ECmiRNA function

Weight loss through low-fat diet resulted in a significant upregulation of 23 ECmiRNA including miR-16, let-7i, miR-26a, miR-17, miR-107, miR-195, miR-20a, miR-25, miR-15b, miR-15a, let-7b, let-7a, let-7c and miR-103 (Hsieh et al., 2015). Target prediction and

pathway analysis on these miRNA revealed that the target genes were predominantly involved in metabolic, insulin signaling, and adipocytokine signaling pathways which are directly linked with pathophysiological changes associated with obesity and weight reduction (Hsieh et al., 2015). On the other hand, high-fat diet led to increasing circulating concentrations of miR-128, miR-130b-3p, miR-374a-5p, miR-423-5p, while an altered expression of miR-128 and miR-130b-3p was observed in both prediabetic and type 2 diabetes subjects compared to control (Prabu et al., 2015). Of those miR-128 was known to be positively correlated with insulin level in circulation. In addition, Povero et al. (2014) showed that nonalcoholic fatty liver disease induced by high-fat diet results in significant enrichment of circulating levels of miR-122 and miR-192 which are previously described in liver disease. Muroya et al. (2015) tried to investigate the potential effect of grazing movement on the ECmiRNA profile in bovine plasma. It is important to note that several circulating miRNA including miR-19b, miR-148a, miR-221, miR-223, miR-320a, miR-361, and miR-486 were found to be differentially regulated, surprisingly, expression of muscle-specific miRNA such as miR-1, miR-133a, miR-206, miR-208a/b, and miR-499 was undetectable in the plasma, although the authors tried to correlate the differential expression of miRNA with grazing exercise there is a possibility that the differential expression of miRNA may due to the freshness of diet (fresh pasture grasses vs. cut pasture grasses). One most recent study demonstrated the intravenous injection of microvesicles coupled with miR-130b reduces epididymal fat deposition in high-fat induced obese mice through the translational repression of PPARγ (Pan et al., 2015).

Exosome mediated release and existence of ECmiRNA is one of the dominant pathways for miRNA to be survived in the harsh condition of circulation. Recently, several studies have shown the importance of exosomal miRNA in diet induced complexities. For instance, exosomal miR-194 plays a crucial role in the cardiac function and mitochondrial activity in high-fat diet-induced mice as well as in human subjects (Nie et al., 2018). The upregulation of exosomal miR-194 was closely related to the impaired cardiac function in human subjects. In addition, it has also been shown that exosomes derived from obese mice are involved in the impairment of mitochondrial activity in myocyte through reduced ATP production (Nie et al., 2018), however, the use of miR-194 sponge improved the cardiac function in in vivo mouse model. Similar studies reported the involvement of exosomal miR-29a (Li et al., 2019) and exosomal miR-122 (Wang et al., 2019) in cardiac function in high-fat diet-induced obese mice and mitochondrial activity in cardiomyocyte. Dietary macronutrient-induced changes in the extracellular miRNA function are presented in Table 5.

3.2.2. Influence of dietary protein on circulating miRNA

In addition to their fundamental role in maintaining nitrogen balance and providing EAA for growth, a growing number of studies indicating that the dietary proteins are directly interacting with a variety of metabolic functions, cellular signaling, and thermogenesis. miRNA are the molecules that fine-tune all these pathways. Given their important role in different physiological processes, extracellular circulating miRNA should have been studied more to understand the effects of dietary proteins. However, unfortunately, there is only one study that evaluated the effect of higher dietary protein intake in the circulating miRNA expression pattern (Ramzan et al., 2019). Because of the fact that high protein diets have a significant impact on the cardiometabolic health of the elderly, the authors used double the recommended protein level for 10 wk to investigate the expression of miRNA in the circulation of the older men. The result was striking. There were 5 miRNA (miR-125b-5p, miR-100-5p, miR −99a-5p, miR-23b-3p, and miR-203a) showed significant downregulation in the study subjects. Bioinformatic analysis revealed that all these miRNA are targeting genes particularly involved in inflammation-related pathways (Ramzan et al., 2019). It is interesting to note that there were very few miRNA showed altered expression, although there was a large change in the dietary protein intake. Therefore, it is not entirely clear whether these alterations in the abundance of circulating miRNA as a result of higher protein intake could actually translate into a physiologically relevant impact on immune cell function.

3.2.3. Carbohydrate regulation of circulating miRNA function

It is extremely important for the elderly to participate in the weight loss interventions as more than 35% of them are obese. Although the short-term energy restriction resulted in improved metabolic and cardiovascular health, it could also lead to undesirable loss of muscle mass. To evaluate whether energy restriction modulates the expression changes of certain miRNA in circulation and whether these changes are associated with the whole-body protein synthesis, Margolis and colleagues recruited 16 overweight older men in a 30% energy restriction regimen for 28 d (Margolis et al., 2017). Energy restriction significantly increased the expression of circulating miR-133a and miR-133b and Backward linear regression analysis revealed that upregulation of myo-miRs was inversely associated with the whole-body protein synthesis. The idea of using circulating miRNA as a potential biomarker to detect the individual with high response to energy restriction-induced weight loss interventions was tested by Parr and colleagues. The authors reported that the expression of circulating

Table 5
Dietary macronutrient induced changes in the expression of extracellular microRNA (miRNA).

Macro-nutrient	Feeding cohort	Organism, tissue/organ	Platform	DE miRNA	Important miRNA	References
Fat	commercial feed, Standard vs. low fat	mice, serum	microarray	28 ↑ 16 ↓	miR-16, let-7i, miR-26a, miR-17, miR-107, miR-195, miR-20a, miR-25, miR-15a, let-7b, let-7a, miR-451, miR-223, miR-92a, miR-200c, miR-873	Hsieh et al. (2015)
Fat	standard vs. high fat	human-mice, serum	miRNA PCR array	–	miR-128, miR-99b-5p, miR-130b-3p, miR-142-3p, miR-374a-5p, miR-423-5p, miR-484, miR-629-5p, let-7d-3p	Prabu et al. (2015)
Fat	standard vs. high fat	mice, plasma exosomes	qPCR	–	miR-194	Nie et al. (2018)
Fat	standard vs. high fat	humans, plasma exosomes	qPCR	–	miR-29a	Li et al. (2019)
Protein	standard vs. high protein	humans, plasma	Next generation sequencing	5 ↓	miR-125b-5p, miR-100-5p, miR-99a-5p, miR-23b-3p, and miR-203a	Ramzan et al. (2019)
Carbohydrate	recommended vs. energy restriction	elderly men, serum	TaqMan miRNA assays	–	miR-1, miR-133a-3p, miR133b, miR-206	Margolis et al. (2017)

DE = differentially regulated; ↑ = upregulated; ↓ = downregulated; let = lethal; qPCR = quantitative PCR.

miR-935 was significantly higher in the low response group compared to the high response group and this miRNA could be a potential biomarker to select the individuals with high response to energy restriction regimen.

4. Conclusion

Over the last decade due to the advancement of omics technology, our understanding of the effect of nutrition on the regulatory mechanisms at cellular and molecular levels has increased at an accelerated rate. A combination of innovative nutritional research and omics technologies will definitely enhance our basic understanding of gene-miRNA-nutrition interactions that ultimately leads to the development of new methods for animal production and disease control. However, this interdisciplinary branch of science is still in its infancy and should walk a long way to debunk the secrets of complex gene–nutrient interactions. Using the available resources, this article showed that there is a direct relationship between the dietary macronutrients and expression of specific genes and miRNA. The obtained information in this article will be immensely helpful to deepen our understanding of dietary macronutrient-induced modulation of gene and miRNA functions as well as the activity of metabolic pathways.

Conflict of interest

The author declares that he has no financial and personal relationships with other people or organizations that can inappropriately influence the work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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