MicroRNA Modulation

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The prevalence of obesity has dramatically increased over the last decades. Weight loss obtained through diet and exercise leads to a significant decrease in morbidity and mortality. Recently, there has been growing interest in the possible beneficial effects of dietary supplements (DSs), including polyphenols, fatty acids, and other plant-derived substances, as adjuvants in the management of obesity and metabolic diseases. Specifically, polyphenols, widely spread in vegetables and fruits, significantly modulate adipose tissue activities, contrasting inflammation and improving insulin sensitivity in preclinical and clinical studies. Remarkably, polyphenols are involved in complex microRNA networks, which play crucial roles in metabolic processes. The administration of different polyphenols and other plant-derived compounds led to significant changes in the microRNA expression profile in peripheral tissues in a growing number of preclinical studies. In particular, these compounds were able to revert obesity-induced microRNA dysregulation, leading to the inhibition of adipogenesis and the induction of weight loss. Furthermore, through microRNA modulation, they attenuated key metabolic alterations, including insulin resistance and lipid anomalies, in animal models of obesity. Some of them were also able to reduce proinflammatory cytokines in adipose tissue. The aim of this review is to summarize current evidence about the effect of plant-derived DSs on microRNA expression in obesity.

Keywords: obesity ; dietary supplements ; diet ; microRNA ; polyphenols ; fatty acids ; weight loss ; obesity treatment ; adipose tissue

1. Introduction

Over the last decades, the prevalence of obesity has consistently grown, becoming a pandemic health concern. It is estimated that obesity and overweight affect up to 50% of the adult population worldwide [1]. Excess body weight is one of the most important risk factors for all-cause morbidity and mortality [2]. In particular, in line with the dramatic spread of these conditions, the occurrence of non-communicable diseases, such as type 2 diabetes (T2D), cardio- and cerebro-vascular diseases (CVD), respiratory diseases, and cancer has consistently risen [3][4][5], accounting for over 80% of all premature deaths [1].

The main treatment strategies to achieve weight loss include lifestyle changes, consisting in promoting healthy dietary patterns to reduce energy intake and enhancing physical activity to increase energy expenditure [6]. Besides lifestyle modifications, several pharmacologic agents are currently available for obesity management, even though conflicting results in terms of efficacy, durability of weight control, and adverse effects have been reported in clinical trials [7]. In spite of the overall improvement in the therapeutic strategies for weight loss, the management of obesity is still challenging. In the last years, the potential role of natural phytochemicals for weight management has gained growing attention [8] and the use of dietary supplements (DSs) as adjuvant treatment for obesity and metabolic diseases has greatly increased [9]. DSs are defined as “products that supplement diet, with or without additional nutritional value, which contain one or more of the following ingredients: a vitamin, a mineral, a herb or other botanical, an amino acid, a dietary substance to supplement diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any reported ingredient” [10][11]. DSs have become an attractive therapeutic option due to their generally low toxicity profile and easy access to the general population.

Over the last decades, there has been growing interest in microRNA, a class of small non-coding RNAs that modulate gene expression, as regulators of metabolic processes and biomarkers of disease. In particular, a wide number of studies have depicted a dysregulation of microRNA expression in obesity and metabolic diseases [12][13][14]. A wide number of dysregulated microRNA target genes involved in pathways critically associated in glucose and lipid metabolism, energy homeostasis, inflammation, immunity, and endothelial function have also emerged, helping unravel the pathophysiological mechanisms underlying obesity and obesity-linked metabolic diseases[13]. Furthermore, circulating and tissue microRNA expression have been found to be significantly modified by different weight loss interventions, including different dietary patterns, physical activity programs, and bariatric surgery [13], suggesting that weight loss and the related metabolic changes might be mirrored by significant modifications in the microRNA signature. Similarly, a wide variety of DSs, such

as polyphenols and other plant compounds, have been shown to regulate microRNA expression in adipose tissue in preclinical models of diet-induced obesity. Therefore, microRNA might be critically involved in the outcome of weight loss interventions. In light of this, a novel approach to obesity treatment is focused on customized nutritional interventions, which take into account not only the phenotype but also genetic and epigenetic data, helping personalize the management of this complex condition [15].

The aim of this review is to summarize the current evidence on the effects of DSs with potential or demonstrated anti-obesity properties on the circulating and tissue microRNA expression profile, to help understand the complex pathophysiological mechanisms underlying obesity and to possibly identify novel candidate biomarkers of metabolic modifications and co-morbidities, such as T2D and hyperlipidemia.

2. General Aspects of MicroRNAs

MicroRNAs are a class of small (19-25 nucleotides), endogenous, and non-coding RNAs that regulate eukaryotic gene expression [16]. They control gene expression via Watson–Crick base-pairing to the 3′ untranslated regions (3′UTRs) of target messenger RNAs (mRNAs) by inhibiting translation and by affecting mRNA stability and degradation [16][17][18]. A single microRNA may target more than 100 mRNAs as well as multiple microRNAs targeting the same gene [19][20].

MicroRNA genes are transcribed by RNA polymerase II (RNA pol II) from intronic regions of non-coding or coding transcripts and exonic regions as longer primary transcripts (pri-miRNAs) and double stranded RNAs (dsRNAs), containing a local stem-loop structure. The pri-miRNA is sequentially cleaved into shorter intermediates by ribonuclease III enzymes: Drosha, Dicer, and dsRNAs-specific nucleases [21][22].

In the nucleus, a heterotrimeric complex termed microprocessor, containing one molecule of the Drosha endonuclease and two molecules of its partner protein Di George syndrome critical region (DGCR8), crops the pri-miRNAs into a shorter hairpin-structured precursor (pre-miRNA) of 65–70 nucleotides in length, bearing 2 nucleotides 3′ overhang, characteristic of RNase III-mediated cleavage. The nuclear transport receptor exportin 5 recognizes the pre-miRNA overhang and mediates the nuclear export of pre-miRNA to the cytoplasm in a Ran-GTP-dependent process, where the pre-miRNA is further processed into a mature miRNA duplex of 22 nucleotides by the RNase III-type endonuclease Dicer in association with TAR RNA-binding protein (TRBP) [23][24]. Following Dicer processing, the miRNA duplex is released and subsequently loaded into argonaute (Ago) family proteins (Ago 1–4 in human) along with chaperone proteins (HSC70/HSP90) to form an effector complex called RNA-induced silencing complex (RISC) in an ATP-dependent manner. The process culminates in the stable association of only one of the two strands with the Ago effector proteins (Ago2). On the basis of the relative thermodynamic stability of the two ends of the microRNA duplex, the less stable strand terminus at the 5′ side will be typically selected as the guide strand, whereas the other strand (passenger strand*) will be degraded [16][21][23]. The mature miRISC recognizes and regulates mRNA target binding by base pairing, with the degree of microRNA-mRNA complementarity being the determinant regulatory mechanism. The perfect complementarity triggers the endonucleolytic mRNA cleavage and the subsequent translation repression, whereas the imperfect one matches mRNA deadenylation and decapping [25].

MicroRNAs exert crucial roles in almost every cellular process by modulating the biological physiologic homeostasis; however, changes in their expression have been observed in human pathologies. MicroRNAs may not only act within cells but also in the extracellular space. Indeed, they have been found in extracellular body fluids, such as serum, plasma, saliva, breast milk, and urine [26].

MicroRNAs are released from cells in membrane-bound vesicles, such as exosomes, microvesicles, and apoptotic bodies, which protect them from blood RNases activity and increase their stability, as well as being associated in complexes with Ago2 proteins or high-density lipoproteins (HDLs) [27][28][29][30].

They act as hormone-like molecules and exert important roles in cell-to-cell communication; these findings have suggested their use as informative biomarkers of physio-pathological status [31].

The pivotal role of microRNAs in metabolic homeostasis and their implication in metabolic diseases (e.g., metabolic syndrome, T2D) has been suggested in several studies.

MiR-122, an abundant liver-specific microRNA, was shown to affect hepatic cholesterol and lipid metabolism, as its inhibition in normal and high-fed mice was associated with a significant reduction in hepatic steatosis and plasma cholesterol levels [32][33]. MiR-33a/b were reported to control cholesterol/lipid homeostasis together with their host gene products, the sterol regulatory element-binding protein (SREBP), through the regulation of the ATP-binding cassette A1 (ABCA1) cholesterol transporter and fatty acid (FA) β-oxidation genes, such as carnitine O-octanoyltransferase (CROT),

carnitine palmitoyltransferase 1A (CPT1A), and hydroxyacyl-CoA dehydrogenase–3-ketoacyl-CoA thiolase–enoyl-CoA hydratase β-subunit (HADHB) [34][35]. Furthermore, the loss of miR-33 leads to the development of obesity and insulin resistance in target tissues, including the liver, white adipose tissue (WAT), and skeletal muscle, in an miR-33 deficient mouse fed a high-fat diet (HFD) [36]. Several microRNAs have been identified to regulate the responses to insulin and glucose homeostasis in the liver, muscle, and adipose tissue. Increased miR-103 and miR-107 expression levels impaired glucose homeostasis and insulin sensitivity in the livers of leptin-deficient (ob/ob) and diet-induced obese (DIO) mice [37]. Similarly, overexpression of miR-143 [38], let-7 [39], and miR-29b [40] has been reported to inhibit insulin signaling and to impair glucose tolerance.

Moreover, numerous microRNAs have been demonstrated to regulate adipocyte differentiation and function [41][42].

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