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MicroRNAs: Decoders of Dysbiosis into Metabolic Diseases?

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Abstract

The identification of molecular factors bridging gut microbiota dysbiosis to alterations of host metabolism still remains a major goal in biomedical research. In fact, on one hand, there is a worldwide consensus about the systemic impact, from brain to liver, from heart to adipose tissue, of gut microbiota dysbiosis. On the other hand, beyond the microbial production of short chain fatty acids and their vast metabolic properties, little is known about the molecular mechanisms linking a change in the activity of gut microbes to a modification of host cell metabolism. In this context, microRNAs (also known as miRs) are promising molecules which could allow explaining how dysbiosis is converted into metabolic outcomes since: 1- miRs are pleiotropic regulators of gene expression, targeting multiple mRNAs at once; 2- miRs expression in specific organs such as the intestine has been demonstrated to be under the control of gut microbiota; 3- alterations in miRs expression have been found in the majority of tissues targeted by gut microbiota dysbiosis during metabolic diseases such as liver, adipose tissue, pancreas, skeletal muscle, intestine, heart and also the brain. In this review publications in the growing field of miRs-based metabolic control at a systemic level will be discussed together with a putative link with gut microbiota dysbiosis.

Keywords: Gut microbiota; Dysbiosis; MicroRNAs; Metabolic diseases; Infections

Introduction

The discovery of the active role of gut microbiota, the trillions of microorganisms inhabiting the gastrointestinal tract of both humans and animals, on whole host metabolism is radically pushing for a new era in medical development, centred on personalized medicine [1].

Recently, the exponential growth of "newly rediscovered" [2] microbial-based therapies such as fecal microbiota transplantation (FMT) for both *Clostridium difficile* recurrent infections [3,4] and metabolic syndrome [5] has demonstrated that gut microbiota represents an effective target for the managing of multiple diseases.

The most striking evidence is related to the fact that gut microbes exert a vast range of metabolic functions, beyond digestion. As a consequence, the alteration, named dysbiosis, of this multifaceted microbial system within our intestine affects host pathophysiology at a multi-organ level [6]. Thus, the growing interest in gut microbiota dysbiosis is based on the experimental evidence that both ecological [7] and functional [8] alterations of gut microbes have a systemic impact on whole host metabolism (Figure 1). Indeed, the metabolic influence of dysbiosis is not limited to a specific period of life, but rather it affects lifespan from childhood to adulthood [9].

Therefore, scientific community is now paying extreme attention to identify the molecular mechanisms by which dysbiosis of gut microbiota alters metabolic pathways of the host. In this context, a huge literature about short chain fatty acids (SCFAs) has flourished in the recent years. In fact, SCFAs, produced by fermentation of complex carbohydrates from plants, have been shown effective in the regulation of crucial functions of the host such as inflammatory response [10], incretins-based control of glucose-tolerance [11] as well as adiposity and energy balance [12], to cite a few. However, when descending at the molecular level of bacteria-to-cell interaction, our knowledge of the complex bidirectional relationship between gut microbiota and the host still has to face its limitations.

Importantly, microRNAs (also miRs) could help deciphering the dialogue between microbes and host cells. Since their discovery in 1993 [13], miRs have held the attention of researchers given their pleiotropic abundance, ranging from plants to animals, and their capacity to regulate gene expression [14]. These tiny molecules of about 22 nucleotides in length belong to the subfamily of small non-coding RNAs such as tRNAs, rRNAs and many others [15], which has to be distinguished from the subfamily of long non-coding RNAs (lncRNAs), longer than 200 nucleotides and without a protein-coding sequence [16]. MicroRNAs are very stable, proposing them as excellent biomarkers for cancer [17] and other diseases such as type 2 diabetes [18]. Of note, a vast range of metabolic pathologies is characterised by alterations in miRs expression in both central and peripheral organs (Figure 1). In this review these alterations will be discussed in both humans and animals and analysed in parallel with gut microbiota dysbiosis associated to pathophysiological modifications in these organs (Table 1).

Putative microbial miRs regulation in dysmetabolism - Focus on: Hepatic and white adipose tissue miRs

The liver and the white adipose tissue (WAT) are crucial organs for the regulation of glucose homeostasis at a systemic level.

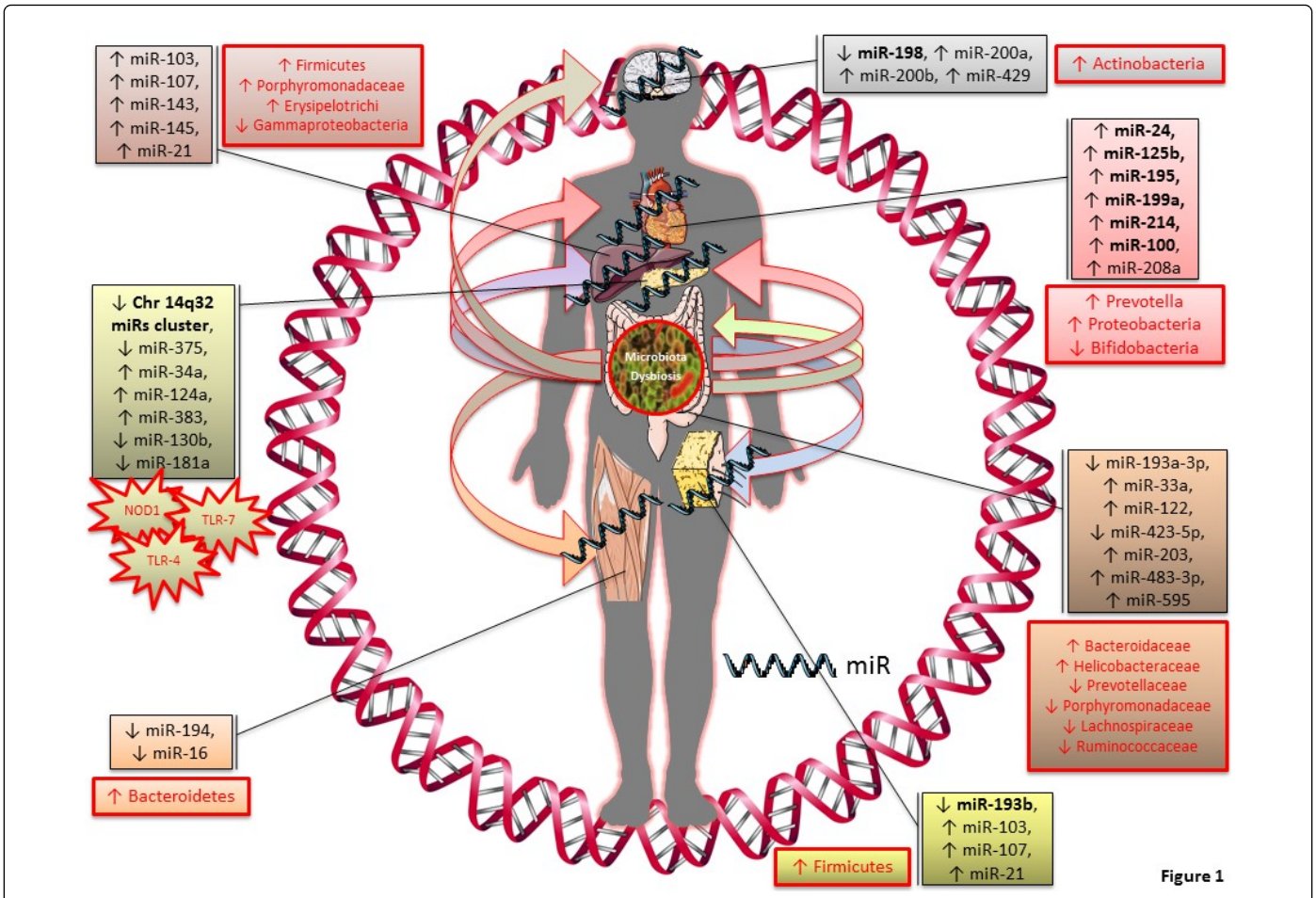

Figure 1: Systemic metabolic overlap at the organ level between gut microbiota dysbiosis and altered miRs expression. The impact of gut microbiota dysbiosis (i.e. induced by a high-fat diet) on whole host metabolism is as inner as capable to affect host pathophysiology at a multi-organ level. Of note, alterations in miRs expression have been found in several tissues targeted by gut microbiota dysbiosis during metabolic diseases such as liver, white adipose tissue, pancreas, skeletal muscle, heart, intestine and brain. These evidences sustain the hypothesis that miRs may be among the molecular factors converting dysbiosis into dysmetabolism at the level of tissue cell. Major miRs discussed in the main text are reported (in bold are miRs found modulated in humans; the others are related to animals; arrows indicate the modulation of miR expression associated to either a given disease and/or observed or putative gut microbiota dysbiosis and the activation of microbial receptors; red-edged rectangles describe observed or putative gut microbiota dysbiosis associated to the related modulation of miR expression).

Nowadays, it has been achieved that both organs are targeted by gut microbiota dysbiosis, which can be related to the expansion of the phylum *Firmicutes* [7] or the family *Porphyromonadaceae* [19].

As for the liver, the gut-to-liver axis plays a fundamental role with regard to the capacity of liver to filter xenobiotics and sense microbial products [20]. Recently, an important role of hepatic modulators has been revealed for bile acids [21], also shown able to impact on miRs expression in human hepatocytes [22] and to play as putative therapeutics in non-alcoholic fatty liver disease (NAFLD) [23], a common feature of metabolic diseases. NAFLD is associated with increased abundance of *Erysipelotrichi* and lower levels of *Gammaproteobacteria* in human stool [24]. In this context, Leti et al. found 30 up-regulated and 45 down-regulated miRs by using high-throughput sequencing to assess miRs obtained from liver biopsies of 15 individuals without NAFLD fibrosis (F0) and 15 individuals with severe NAFLD fibrosis or cirrhosis (F3-F4) [25].

As for the human WAT, numerous miRs exist but only a few number is altered in obesity and type 2 diabetes mellitus such as miR-193b, whose expression correlates positively with adiponectin gene expression and negatively with homeostasis model assessment of insulin-resistance [26].

In mice, the up-regulation of miR-103 and miR-107 was observed in obese mice and gain of function of both miRs in the liver and WAT impairs glucose metabolism [27]. By contrast, silencing of miR-103 and miR-107 improves insulin-sensitivity [27]. The expression of two other miRs, miR-143 and miR-145, is increased in the liver of both genetic and nutritional murine models of obesity [28].

Organ	miR modulation	Text reference	Associated dysbiosis/microbial receptor activation
Liver	↑miR-103, ↑miR-107	27	↑ *Firmicutes* ↑ *Porphyromonadaceae* ↑ *Erysipelotrichi* ↓*Gammaproteobacteria*
	↑miR-143, ↑miR-145	28	
	↑miR-21	30, 31, 32	
White adipose tissue	↓miR-193b	26	↑ *Firmicutes*
	↑miR-103, ↑miR-107	27	
	↑miR-21	30, 31, 32	
Pancreas	↓Chr 14q32 miRs cluster	40	NOD1, TLR-4, TLR-7
	↓miR-375	41,42	
	↑miR-34a, ↑miR-124a, ↑miR-383, ↓miR-130b, ↓miR-181a	43	
Heart	↑miR-24, miR-125b, ↑miR-195, ↑miR-199a, ↑miR-214	54	↑ *Prevotella* ↑ *Proteobacteria,* ↓ *Bifidobacteria*
	↑miR-100	55	
	↑miR-208a	62	
Skeletal muscle	↓ miR-194	64	↑ *Bacteroidetes*
	↓miR-16	65	
Brain	↓miR-198	70	↑ *Actinobacteria*
	↑miR-200a, ↑miR-200b, ↑miR-429	75	
Gut	↓miR-193a-3p	82	↑ *Bacteroidaceae* ↑ *Helicobacteraceae* ↓ *Prevotellaceae* ↓ *Porphyromonadaceae* ↓ *Lachnospiraceae* ↓ *Ruminococcaceae*
	↑miR-33a, ↑miR-122	83	
	↓miR-423-5p	85	
	↑miR-203, ↑miR-483-3p, ↑miR-595	86	

Table 1: Organ-specific miR expression modulation and associated gut microbiota dysbiosis.

These two miRs act like a cluster, therefore, mice deficient for both miR-143 and miR-145 are protected from obesity-related comorbidities such as insulin-resistance. However, only the overexpression of miR-143, but not that of miR-145, is able to impair AKT-mediated insulin-signalling and thus glucose homeostasis.

Another important factor regulating adiposity and hepatic metabolism is miR-21, known as a disease-linked miR [29]. The team of Prof. Dimmeler recently showed that the long-term (18 weeks) inhibition of miR-21 is effective to reduce body weight and adipocyte size in aged db/db mice [30], whereas in the liver miR-21 regulates both regeneration [31] and progression of fibrosis [32]. With regard to the impact of miRs expression on hepatic metabolism also contradictory results can be found. In fact, it has been shown that the hepatocyte-specific deletion of the miR-processing enzyme Dicer1 has either no impact on the hepatic function [33] or promotes hepatocarcinogenesis in mice [34]. Indeed, both liver [19,35,36] and adipose tissue [37-39] have been shown to be specifically and deeply targeted by dysbiosis of gut microbiota, as reported above.

These evidences strongly suggest the association between a change in miRs expression and the impact of gut microbiota dysbiosis for the control of both hepatic and WAT metabolism.

Pancreatic miRs

Interestingly, alterations of miRs expression can also be found at the level of the pancreas, a crucial organ exerting the maintenance of glucose homeostasis by secreting insulin and glucagon.

In humans, Kameswaran et al. described a cluster of miRs in an imprinted locus on human chromosome 14q32. This locus is highly and specifically expressed in human beta-cells and is intensely downregulated in islets from diabetic donors [40].

In mice, the high expression of miR-375 was shown important for the normal pancreatic alpha- and beta-cells mass [41] as well as for the regulation of insulin secretion [42]. Moreover, an ageing-associated upregulation of miR-34a, miR-124a and miR-383, and downregulations of miR-130b and miR-181a were found in the pancreas of 12-month-old rats [43]. Importantly, besides the well-

established age-induced modification of gut microbiota [44], clear evidences between the link of pancreas health and sensing of microbial antigens have been provided by several publications. In fact, in this context, the NOD1-mediated experimental pancreatitis [45], the impact of TLR-4 on the severity of acute pancreatitis and pancreatitis-associated lung injury in mice [46] as well as the impact of TLR-7 on pancreatic carcinogenesis both in humans and mice [47] have been demonstrated. Thus, it appears clear that a dysbiosis-induced altered production of multiple microbial antigens such as peptides derived from bacterial cell wall and containing for instance D-glutamyl-meso-diaminopimelic acid (iE-DAP) moiety (recognized by NOD1), lipopolysaccharides (LPS, recognized by TLR-4) and single-stranded microbial RNA (recognized by TLR-7) may drive pancreatitis.

Again, these evidences converge towards the association between altered miRs expression and gut microbiota dysbiosis to modulate pancreatic functions.

Cardiac miRs

Recently, the microbial activity has been shown effective in promoting cardiovascular diseases *via* a mechanism based on the metabolism of phosphatidylcholine [48]. Nevertheless, contrasting results can be found in the literature with regard to the metabolic impact of microbial-generated metabolites from phosphatidylcholine, such as trimethylamine (TMA) and TMA-N-oxide (TMAO) [49]. In detail, regarding the human enterotype classification [50], the enterotype *Prevotella* is associated with higher blood levels of TMAO than the enterotype *Bacteroides* in humans [51]. With regard to the cardiac metabolism in a context of gut microbiota dysbiosis, we showed that the severity of cardiac metabolism in a murine model of metabolic adaptation to a high-fat diet [52] is associated to a specific periodontal microbiota characterized by a 37% abundance of *Proteobacteria* [53]. Thus, these data suggest a link between periodontal microbial activity and heart pathophysiology.

With regard to cardiac miRs, in humans, an altered expression has been found for mir-24, miR-125b, miR- 195, miR-199a and miR-214 in the human left ventricle when comparing samples from control and ischemic cardiomyopathy, dilated cardiomyopathy or aortic stenosis groups [54]. Matkovich et al. also reported, by microarray profiling of miRs, an upregulation for mir-100 and miR-195 in human heart tissues (myocardial specimens) in clinical and experimental congestive heart failure (CHF) [55]. Of note, all the above reported cardiovascular diseases are strongly associated with metabolic diseases, as well known.

Recently, soluble ST2 (suppression of tumorigenicity 2) has emerged as novel cardiac bio-marker, especially in heart failure and ischemic heart diseases [56]. Soluble ST2 is a blood protein which acts as a decoy receptor for IL-33, limiting IL-33 interaction with ST2 ligand [57]. Notably, the induction of IL-33 by the gut microbiota has been recently shown in a model of inflammatory bowel diseases [58], characterized by several dysbioses such as a *Bifidobacteria* decrease [59] or an increase in *Proteobacteria* [60]. Finally, Xiang et al. published that miR-487b acts as a negative regulator of macrophages activation by targeting IL-33 production [61]. Thus, these experimental evidences show the inner link between gut microbiota and the regulation of miRs expression for the control of pathophysiological manifestations.

Importantly, considering that dysbiosis has been primary identified and extensively studied in diabetes and obesity, strong risk factors for cardiovascular diseases, and taking into account the role of gut microbiota in the modulation of energetic metabolism [37], the work from Grueter et al. suggests a bridge between gut microbiota dysbiosis and cardiac metabolism *via* miRs expression. In fact, the authors found that a cardiac-specific microRNA, miR-208a, is able to negatively regulate MED13, a subunit of the Mediator complex, resulting in diminished energy expenditure [62]. Altogether, these experimental evidences propose that an altered miRs expression and gut microbiota dysbiosis meet to manage the pathophysiological status of a given organ.

Skeletal muscle and miRs

Among the main effects of gut microbiota on whole host physiology is the up-regulation of the energetic metabolism. In fact, Backhed et al. showed that the resistance of axenic mice to diet-induced obesity is associated with hepatic and skeletal muscle increased levels of phosphorylated energetic intracellular sensor AMP-activated protein kinase (AMPK) and its downstream targets Acetyl-CoA carboxylase and Carnitine-palmitoyltransferase, positive regulators of fatty acid oxidation [38]. Thus, this work firstly provided the existence of a gut-to-skeletal muscle axis. A vast body of evidences in the scientific literature shows the relationship between metabolic diseases and altered muscle metabolism. For instance, Kase et al. showed that myotubes from obese/diabetic patients had lower lipolysis (-30%/-40%) when compared to lean subjects, together with a lower insulin-stimulated glycogen synthesis (-60%) and AKT phosphorylation (-90%) [63]. In this context, it has been recently shown that Type 2 Diabetes mellitus is associated with regulation of several miRs in the skeletal muscle. Latouche et al. identified miR-194 as the sole miR whose expression was reduced across different phases of the disease progression, from an early insulin-resistance to the establishment of diabetes [64]. In Zucker rats, Lee et al. found almost a 50% reduction in the expression of miR-16, controlling the accretion of skeletal muscle protein, during insulin-resistance, when compared to lean rats [65].

Importantly, in the absence of obesity, both T2D patients [66] and mice [52] display a dysbiosis dominated by the phylum *Bacteroidetes*, which therefore is in association with the above reported miRs profiling.

Brain and miRs

Of note, beyond peripheral organs, also the brain is affected by miRs alterations. Moreover, gut microbiota has been shown to correlate to and affect both cerebral structure and behaviour in humans, where the phylum *Actinobacteria* was associated with functions of the thalamus, hypothalamus and amygdala [67] and mice [68,69]. In humans, there is a rich literature regarding the role of miRs in human glioma. For instance, Man et al. found a significant down-regulation of miR-198 expression in 122 pairs of human gliomas compared with corresponding non-neoplastic brain tissues. Also reduced levels of miR-198 were associated with a higher WHO grade and lower Karnofsky performance status (KPS) score. Finally, overexpression of miR-198 in U87 cells reduced cell proliferation, increased cell apoptosis and repressed both cell invasion and migration [70]. Altogether, these data suggest that miR-198 may act as a tumor suppressor, proposing miR-198 as a new target for molecular therapies in human glioma and opening the route towards the study of gut microbiota dysbiosis in this disease.

Importantly, the energetic metabolism can bridge the above reported pathology with both metabolic effects and gut microbial activity. In fact, Adeberg et al. reported that metformin is associated with prolonged progression-free survival in diabetic glioblastoma patients [71]. Notably, numerous experimental evidences link the metabolic effects of metformin with gut microbial modulation in both humans, where metformin increased the abundance in *Escherichia spp.* and lowered *Intestinibacter* in T2D [72] and animals, such as *Caenorhabditis elegans*, by altering folate metabolism and methionine cycle of *E. coli* [73]. Finally, metformin was shown effective in targeting miRs expression in diabetic subjects [74], closing the circle between brain, metformin, gut microbes and miRs.

In animals, miR-200a, miR-200b and miR-429 are up-regulated in the hypothalamus of ob/ob mice. A leptin treatment is able to down-regulate the expression of these miRs and the silencing of miR-200a is effective against body weight gain, restoring hepatic insulin-sensitivity [75]. The team of Prof. Pettersson was the first to show that a normal gut microbiota is able to modulate both brain development and behaviour [69]. Subsequently, Hsiao et al. published an elegant work showing that gut microbiota is able to modulate behavioural and physiological abnormalities associated with neurodevelopmental disorders in the field of autism [76]. Importantly, obese-type dysbiosis is able to induce neurobehavioral changes even regardless of the driver pathology, as observed for obesity [77]. Recently, Braniste et al. published that gut microbiota influences the permeability of blood-brain barrier in mice [68], showing that both intestinal [78] and central permeability are under the control of gut microbes. Therefore, to the light of the aforementioned evidences, it appears likely that a link may exist between gut microbiota and miRs, two main modulators of brain function.

Gut microbiota and miRs modulation: From association to causality?

The work from Dalmasso et al. provided a first experimental proof for a direct link between gut microbiota and the regulation of miRs expression. In fact, by comparing axenic vs. conventionalized mice, the authors showed that both in the ileum and the colon the expression of specific miRs was under the control of gut microbiota [79]. Still focusing on intestinal miRs, Liu et al. demonstrated that gut miRs synthesis from the host is effective in regulating gut microbiota dysbiosis. The authors developed a mouse model with no mature miRs all along the intestinal tract, by using a gut-specific deletion of Dicer1, the miR-processing enzyme, already mentioned above [33,34]. As a consequence, these mice had no fecal miRs and developed exacerbated dextran sulfate sodium (DSS)-induced colitis, displaying gut microbiota dysbiosis with increased *Bacteroidaceae* and *Helicobacteraceae* and decreased *Prevotellaceae*, *Porphyromonadaceae*, *Lachnospiraceae* and *Ruminococcaceae* families [80]. Thus, this work proposes intestinal miRs as important molecules capable to exert a selection pressure on gut microbiota ecology, limiting uncontrolled microbial overt-abundance and hence gut microbiota dysbiosis. This latter property appears to be based on the capacity of miRs to enter bacteria and directly impact on microbial metabolism. In accordance with the aforementioned work, Singh and colleagues found that caecal miRs profile depends on the presence of the endogenous gut microbiota in mice [81].

To sustain the evidence that gut microbiota may impact on host pathophysiology based on a change on miRs profile, Dai et al. recently published that miR-193a-3p is able to reduce colonic inflammation in response to gut microbiota *via* a down-regulation of PepT1, a di/tripeptide transporter that uptakes bacterial product [82]. Moreover, Baselga-Escudero et al. reported normalized liver miR-33a and miR-122 levels in high-fat diet-induced obese rats treated with a low dose of proanthocyanidins [83]. These compounds are the most abundant flavonoids in the human diet, and their beneficial effect may rely on the microbial catabolism leading to the subsequent release of absorbable metabolites [84].

The modulation of miRs expression can also be one of the putative mechanisms of action of probiotics, as proposed by Kreuzer-Redmer et al. The authors analyzed the expression of both miRs and their potential target genes in the jejunum and ileum from *Enterococcus faecium* NCIMB 10415-fed piglets versus untreated controls. The main datum reveals a 2.11-fold increase of miR 423-5p and the related downregulation of the immune-relevant immunoglobulin lambda light C region (IGLC) and immunoglobulin kappa constant (IGKC) target genes [85]. On the same direction, Veltman et al. profiled miRs from T84 monolayers before and after co-incubation with *E. coli* Nissle 1917. The authors revealed for the first time miRs differentially regulated such as miR-203, miR-483-3p and miR-595 targeting tight junction proteins [86]. Of note, inhibition of these miRs blunted the disruption of tight junctions induced by enteropathogenic *E. coli* (EPEC). Thus, the important message of this work is that the probiotic effect of *E. coli* Nissle 1917 on T84 epithelial cells may be recapitulated by the action of these specific miRs on T84 cells.

Conclusion and Future Directions

The experimental evidences underlined in this review strongly push to join dysbiosis and modulation of miRs expression for the control of systemic metabolism.

The discovery of the molecular basis underlying the link between gut microbiota dysbiosis and the modulation of whole host metabolism may have a huge impact on the management of the pandemic of metabolic diseases. Furthermore, the microbial universe within the intestine appears to hide a molecular microcosmos inside, since it has been observed that also bacteria can synthesize miRs [87]. Indeed, microbial miRs seem to have broader functions than eukaryotic ones, since they can promote both degradation and stabilization of the targeted mRNAs, such as GadY, a small (59 to 105 nucleotides) RNA regulating acid response genes in *E. coli* [88].

Thus, deciphering the molecular dialogue between microbes and host may provide innovative targets allowing new therapy developed. To the light of this hope, miRs represent promising molecules which may link the intricacy of gut microbial ecosystem to systemic metabolic outcomes arising from gut microbiota dysbiosis. To shed light into this path, more studies are needed to finally validate the direct link between a change in gut microbial ecology and the concomitant modulation of tissue miRs expression for the control of host pathophysiology.

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Competing Interest

No competing interest exists.

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