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Review Article

Gut microbiota—a positive contributor in the process of intermittent fasting-mediated obesity control

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ABSTRACT

Historically, intermittent fasting (IF) has been considered as an effective strategy for controlling the weight of athletes before competition. Along with excellent insight into its application in various spaces by numerous studies, increasing IF-mediated positive effects have been reported, including anti-aging, neuroprotection, especially obesity control. Recently, the gut microbiota has been considered as an essential manipulator for host energy metabolism and its structure has been reported to be sensitive to dietary structure and habits, indicating that there is a potential and strong association between IF and gut microbiota. In this paper, we focus on the crosstalk between these symbionts and energy metabolism during IF which hold the promise to optimize host energy metabolism at various physical positions, including adipose tissue, liver and intestines, and further improve milieu internal homeostasis. Moreover, this paper also discusses the positive function of a potential recommendatory strain (*Akkermansia muciniphila*) based on the observational data for IF-mediated alternated pattern of gut microbiota and a hopefully regulatory pathway (circadian rhythm) for gut microbiota in IF-involved improvement on host energy metabolism. Finally, this review addresses the limitation and perspective originating from these studies, such as the association with tissue-specific bio-clock and single strain research, which may continuously reveal novel viewpoints and mechanisms to understand the energy metabolism and develop new strategies for treating obesity, diabetes, and metabolic disorders.

1. Introduction

Food restriction has been considered as a simple and straightforward strategy for restricting energy uptake since the well-known establishment of the viewpoint that obesity is actively responsible for multiple metabolic diseases (de Cabo et al., 2014; Hatting et al., 2017; US Preventive Services Task Force; et al., 2018). Compared to increasing energy expenditure through physical exercise, fasting-mediated energy restriction is an easier strategy to trial for most individuals (Hatting et al., 2017). Among various fasting modes, intermittent fasting (IF) has gradually attracted increasing attention, for it not only provides energy restriction but also avoids long-term fasting-mediated injury of the gastrointestinal tract (Hatting et al., 2017).

Currently, the endemic obesity epidemic has given rise to the development of new and effective dietetic solutions, which has resulted in the revealing of the mechanism of IF-mediated positive influence (Bartosz Malinowski et al., 2019; Johnstone, 2014). For most mammals, the limitation of IF is lower than traditional calorie restriction (Barnosky et al., 2014; Hwangbo et al., 2020). There are 2 basic strategies of IF: time-restricted feeding and alternate-day fasting (Barnosky et al., 2014; Carter et al., 2016; Johnstone, 2014; Tinsley and La Bounty, 2015). In the various protocols of alternate-day fasting, the main documented systems are “5:2” and “4:3”, of which the first figure represents the number of regular diet days and the second figure indicates fasting days (Bartosz Malinowski

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et al., 2019). Compared to continuous energy restriction, IF has been found to be more effective in the 5:2 system (Carter et al., 2016). Carter et al. (2016) determined that IF treatment contributed to decreasing weight and controlling hyperglycemia, which was better than continuous energy restriction, indicating that IF seemed a better strategy for treating obesity. A previous study demonstrated that IF administration not only rebounded hunger during fasting days but also increased satiety after a meal, resulting in the inhibition of dietary consumption (Heilbronn et al., 2005). Furthermore, IF can be successfully implemented in a population of patients with type 2 diabetes (T2D) (Jane et al., 2015). In recent years, multiple findings have presented in this space and explained this administration from different perspectives, indicating that IF contributes to triggering various protective mechanisms from obesity and related metabolic syndrome (Chaix et al., 2019; Mitchell et al., 2019). Even more novel findings are expected in terms of regulatory analysis of these complex and variable datasets. However, we focused on the role of gut microbiota in IF-mediated host metabolic improvements in this review.

Gut microbiota involves major energy metabolic processes (Bohan et al., 2019). Enteric dysbiosis is a well-established biomarker for many energy dysmetabolism-induced chronic diseases, including excess adiposity, diabetes, and other metabolic syndrome (Bohan et al., 2019). Throughout recent decades, with continuous studies on the relationship between host energy metabolism and gut microbiota, although there are occasional controversies (Wu et al., 2011; Zhao et al., 2018), diet-induced alterations of microbial communities have been considered to be one of the crucial regulatory factors, as the composition of the microbial communities is highly sensitive to the host dietary structures or habits (Barton et al., 2018; Bowyer et al., 2018; Le Chatelier et al., 2013; Wu et al., 2011). Therefore, IF-mediated large amplitude changes occurring in host energy metabolism are easier to link with gut microbiota (Maria Carlota Dao et al., 2016; Li et al., 2017). In other words, gut microbiota virtually plays a vital role in IF-mediated host energy control.

This review aims to summarize the published mechanisms by which these symbionts affected host energy metabolism under IF condition during the past 4 years. First, the paper discusses the potential of gut microbiota as a measurable indicator for IF, which might open a new research perspective for this field and avoid some errors originating from various physiological structures. In the second part, this review addresses the physiological functions of gut microbiota in IF-mediated improvements at various peripheral tissues/organs which play important roles in energy metabolism, including intestines, liver, pancreas, and adipose tissue. Moreover, in this review we summarize a potential recommendatory strain, *Akkermansia muciniphila*, which has been found to be positively associated with IF-mediated improvements on energy metabolism, and a hopeful regulatory pathway (circadian rhythm) that was considered to be a link between the microbe and IF. Finally, we address some limitations and perspectives in this field, which may provide some insight into further studies.

2. Gut microbiota—a hopeful bio-marker for evaluating IF-mediated beneficial effects

In a broad sense, IF comprises multiple individual protocols (Tinsley and La Bounty, 2015). However, there is an enduring theme that the fasting period should be longer than overnight, whereas the other attributes are flexible (Cignarella et al., 2018; Hatting et al., 2017; Li et al., 2017, 2018; Tinsley and La Bounty, 2015). It must be mentioned that a fasting protocol may not lead to the same positive modulations on different animal models or subjects, indicating that there are great individual differences (including species difference) in IF-mediated physiological improvements (Heilbronn et al., 2005; Varady et al., 2008). Thus, the identification of a new quantifiable bio-marker is able to further provide a novel perspective for rapidly evaluating beneficial effects (Barton et al., 2018; Bohan et al., 2019; Cignarella et al., 2018; Maria Carlota Dao et al., 2016; Hatting et al., 2017; Le Chatelier et al., 2013; Li et al., 2017; Wu et al., 2011). This quantifiable bio-marker should include following points: (1) sensitivity to alteration in dietary structure and habits and high association with energy metabolism; (2) wide expression in various animals; (3) high conservation among various animals, at least in the same species (Bohan et al., 2019; Secor and Carey, 2016; Thorens, 2015; Walter et al., 2020). Taken together, gut microbiota seems to be a potentially hopeful target for evaluating IF-mediated beneficial effects (Barton et al., 2018; Bohan et al., 2019; Cignarella et al., 2018; Maria Carlota Dao et al., 2016; Le Chatelier et al., 2013; Li et al., 2017; Wu et al., 2011).

In a natural environment, the digestive tract of most animals is a colonized microbe that contains an abundant microbiome (more than 100 trillion species) and genetic material (3 million genes) (Qin et al., 2010). A dense microbial community is a colonist in the gastrointestinal tract (Bohan et al., 2019). This so-called “co-evolution” of host-microbiome is acritical part of biology (Groussin et al., 2020). Therefore, it is considered a mutualistic symbiosis interrelationship between the microbiome and its host (Groussin et al., 2020). From a positive perspective, the intestine and gut microbiota are mutually beneficial: the former provides a suitable living environment for microbiota, while the latter feeds back with essential functions, such as assisting the development of the immune system and preventing intestinal infections (Groussin et al., 2020). Given the universality of microbial symbionts to their colonization in the host digestive tract, including invertebrates and vertebrates, the gut microbiome is an eligible candidate that reflects the IF-mediated physiological state, especially in the same species (Catterson et al., 2018; Cignarella et al., 2018; Hatting et al., 2017; Li et al., 2017).

The gut microbial composition is susceptible to dietary structure and host physiological activities. The regular patterns of the microbial community are closely associated with host health status (Bohan et al., 2019). Gut microbiota, over the during decades, has become a hot spot for investigation as a significant contributor to host metabolism and immunity, including digestive absorption, nutrition intake, synthesis of vitamins, and prevention of pathogen colonization (Isabel Moreno-Indias et al., 2014; Kamada and Nunez, 2013). Inversely, obesity-induced enteric dysbacteriosis might be responsible for obesity, local and systematical inflammation (Frank et al., 2007; Qin et al., 2012; Turnbaugh et al., 2006). Gut microbiota—host interactions are built on multiple signal pathways and a series of bio-molecules (Frank et al., 2007; Qin et al., 2012; Turnbaugh et al., 2006). In addition to nutritional intervention (dietary structure)-triggered alteration of gut microbial composition, feeding behavior has also been reported to restructure the microbial community in the intestines (Sonoyama et al., 2009). For instance, the discovery of discrepant abundances of *A. muciniphila* between individuals with/without obesity is undoubtedly a significant academic achievement (Collado et al., 2010; Derrien et al., 2004; Everard et al., 2013). Subsequent studies have also demonstrated that this microbe alleviates multiple energy dysmetabolism-induced organ/systemic diseases, whereas the lower abundance of *A. muciniphila* positively correlates with hyperlipidemia, T2D, and fatty liver (Everard et al., 2019; Plovier et al., 2017; Roopchand et al., 2015). Moreover, the research pertaining to *A. muciniphila* is not limited to this field, but also extends to other disease preventions such as progeria and multiple sclerosis (MS) (Bárcena et al., 2019; Cekanaviciute et al., 2017). Notably, the high abundance of this strain is, in part, positively associated with IF treatment based on several

published papers, suggesting that gut microbiota holds huge potential for reflecting IF-mediated positive influence (Barton et al., 2018; Maria Carlota Dao et al., 2016; Li et al., 2017). Meanwhile, this phenotype appears to be conservative among various animals (it has also been shown in Burmese pythons, drosophila, fish, murine, canine, Syrian hamsters, and human) (Costello et al., 2010; Greer et al., 2016; Kasiraj et al., 2016; Li et al., 2019; Sonoyama et al., 2009). These findings provide hard evidence to support the rationality and the potential of gut microbiota in the development of a bio-marker for IF treatment, especially the investigation of the function of single strain.

3. Insights into IF-mediated positive effects on energy metabolism via shaping gut microbiota

Many efforts over past decades have gradually furthered our concerns on the importance of maintaining the balance among intestinal bacterial communities, because it has been regarded as a key link for host metabolism and health (Frank et al., 2007; Turnbaugh et al., 2006). In reverse, enteric dysbacteriosis is associated with the alternation of microbial metabolite components and other products that lead to obesity and other related diseases (Turnbaugh et al., 2006). Hence, the functional role of gut microbiota has attracted increasing attention as a potential bio-marker for representing various physiological or pathological states (Catterson et al., 2018; Cignarella et al., 2018; Hatting et al., 2017; Li et al., 2017).

A major finding in this space has come from the observation of intestinal microbe-mediated regulation of myocardial ketone body metabolism in mice during fasting (Crawford et al., 2009). This was revealed in mice via the comparison of the gut microbial ecology and myocardial ketone body metabolism in fasted state within feeding state and germ-free conditions (Crawford et al., 2009). In this research, Crawford et al. (2009) demonstrated that the expression of a fasting gut microbial community-dependent hepatic ketogenesis was increased, which directed the myocardial metabolic pattern into ketone body utilization. However, germ-free mice sustained their heart rate through elevating glucose consumption during fasting, and many ketone body metabolism-generated improvements were not observed (Crawford et al., 2009). These findings indicate a vital role of gut microbiota in fast-mediated host metabolic transformation and open a new research perspective for this field. Hence, research regarding the relationships between gut microbiota and host physiology during IF has gradually become a hot point (Li et al., 2016; Zarrinpar et al., 2014).

While we have emphatically discussed the functional mechanisms of gut microbiota during IF-mediated obesity control and its potential relevance of various physiological aspects from peripheral tissues/organs which are strongly associated with energy metabolism, considering the vital role of the central nervous system (CNS), especially the brain, in maintaining energy metabolic balance and close relationship with gut microbiota, the impact of gut microbiota on CNS under IF administration was also addressed.

3.1. Gut microbiota involves in maintaining the metabolic homeostasis of adipose tissue during IF

The research regarding IF as an effective strategy of energy restriction has made considerable progress in the field of adipose tissue over the past 4 years (Bartelt et al., 2018; Cushing et al., 2017; Hatting et al., 2017; Iwakoshi-Ukena et al., 2017; Kim et al., 2017; Li et al., 2017, 2018). In mammals, adipose tissue is susceptible to changes in energy requirement and possesses considerable capacities to remodel energy homeostasis (Bartelt et al., 2018). Based on this physiological property of adipose and the operability of IF in reality, Hatting et al. (2017) performed a series of experiments to investigate the energy expenditure of brown adipose tissue (BAT) during IF in high fat diet-raised mice. By using gene knockout mice, they claimed that CDC-like kinase 2 was a key regulatory molecular in BAT-mediated thermogenesis during IF through driving high-level expression of uncoupling protein 1 (UCP1) (Hatting et al., 2017). Due to technological constraints, they did not further determine whether this modulation was BAT-specific and not evidenced in white adipose tissue (WAT) (Hatting et al., 2017). Thus, the development of relative tissue-specific gene knockout mice will be a focus in their future studies (Hatting et al., 2017). The same year, another group determined neurosecretory protein GL (NPGL) as a novel signaling molecule that increased food uptake and WAT expansion (Iwakoshi-Ukena et al., 2017). Interestingly, fasting-induced low-level of insulin also up-regulates its expression, suggesting that neurosecretory protein GL may play an essential role in energy preparation during negative energy state (Iwakoshi-Ukena et al., 2017). Moreover, Martinez-Lopez et al. (2017) sketched the pattern of IF-derived tissue-specific autophagy and other positive effects on the improvement of metabolic syndrome.

Among various studies, one important finding is the definition of the gut microbiota as a potential manipulator for energy metabolism in mice under IF treatment (Li et al., 2017). This result opens a new perspective to determine IF fasting-mediated positive influences. Pertaining to the gut microbiota, evidence for host energy administration has been widely reported, but its role in IF-mediated energy optimization is rarely a focus (Bohan et al., 2019). Under IF background, Li et al. (2017) successfully detected the reversion of metabolic homeostasis and gut microbial depletion-induced WAT being inhibited by using the classical fecal microbiota transplant (FMT) in germ-free mice, indicating that gut microbial remodeling by IF was required for maintaining host energy metabolic homeostasis. Interestingly, IF-activated CDC-like kinase 2 (CLK2)-cyclic AMP response element binding protein (CREBP)-UCP1 pathway mediated the high expression of UCP1, enhanced BAT thermogenesis, and promoted a healthy adipose tissue metabolic phenotype, which has been found to be dependent on remodeling of the gut microbiome (Li et al., 2017). However, this investigation did not go beyond total microbiome analysis, and did not further determine the functional effects of single or a few numbers of bacterial strains, and did not definitely establish an integrated regulatory circuit originating from these symbionts to target organ or tissue (Li et al., 2017). In addition to promoting energy expenditure in the adipose tissue, IF may exert a potent immunomodulatory influence and contribute to modulating adipokines secretion partly through the gut microbial pathway (Cignarella et al., 2018). In a clinical study, 16 patients with MS were assigned to 2 groups which respectively received intermittent energy restriction (IER) and ad libitum treatments after controlling baseline (Cignarella et al., 2018). After 15 d, the level of serum leptin was found to be obviously reduced in IER group. Meanwhile, adiponectin was greatly elevated in treatment, although there was no statistical difference to the control (Cignarella et al., 2018). In line with this, simultaneous testing using a mouse model confirmed this change, and subsequent FMT further demonstrated that gut microbiota was to partly involved in this regulation (Cignarella et al., 2018). Overall, gut microbiota should be considered as an important link in IF-mediated regulatory circuit from host intestines to adipose tissue.

3.2. IF improves enteric health through gut microbiota

Another action site of IF is the intestine (Greer et al., 2016; Li et al., 2019; Wei et al., 2018a). Indeed, the gut should be a concern because

of its physical position where it is directly exposured to the intestinal microbiota (Bohan et al., 2019). During past 4 years, investigations from published data suggest that the gut microbiota plays multiple roles in IF-mediated energy metabolic optimization via enterohepatic pathways, including intestinal barrier protection, hepatic metabolism reprogramming, and lifespan extension (Greer et al., 2016; Li et al., 2019; Wei et al., 2018a). For example, in a study by Catterson et al. (2018), they further determined gut microbial abundance as an important factor after the detection of the improvement of intestinal barrier integrity under IF treatment. Compared with the control, *Lactobacillus-plantarum*, one of the most abundant bacteria and a commensal negatively associated with gut barrier function, was found to be significantly inhibited in fruit fly form IF groups, suggesting that IF might improve intestinal health via alleviating high abundance of the gut microbiota-mediated defensive load (Catterson et al., 2018). Meanwhile, this research also offered evidence to demonstrate that IF-mediated various positive effects on the fly at the different growth stages, including energy metabolism and lifespan extension (Catterson et al., 2018). Although this group did not continue to investigate the crosstalk among microbe, gut, and lipometabolism in their paper, we believe that there were still some novel linkages that need to be explored.

Inflammatory bowel disease (IBD), a chronic intestinal illness including Crohn's disease and ulcerative colitis, has been considered to result from complex factors (Singh et al., 2017). Of note, recent clinical data show that incidence of IBD is climbing in parallel with increasing number of patients with obesity, indicating that IBD may become a vital risk of the occurrence of obesity (Singh et al., 2017). Beyond the abundant epidemiological association and immune interaction between intestinal microbiome and gut, the elevated prevalence of obesity in patients with IBD implies that there is a serious energy dysmetabolism (Singh et al., 2017). In view of this, one could expect energy controls (such as IF) to be a new effective strategy for alleviating inflammation and obesity (Liu et al., 2017; Shojaie et al., 2017). Remarkably, Rangan et al. (2019) has reported a close association between gut microbiota and host intestinal immunity. In this study, dextran sodium sulfate-induced IBD pathological model (mouse) was subjected to IF treatment and showed significant alleviation of intestinal inflammation (Rangan et al., 2019). Furthermore, this treatment also increased gut repair capacity through promoting the proliferation of colonic stem cells (Rangan et al., 2019). Of note, these improvements would be represented by FMT from wild mice to pathological model, whereas retrorse FMT resulted in inflammatory occurrence (Rangan et al., 2019). These findings indicate that the special pattern of gut microbiota not only represents corresponding physiological status but also enables the inheritance/delivery of it, resulting in phenotypic recurrence under IF.

3.3. What is the role of gut microbiota in IF-mediated metabolic improvements in liver and pancreas?

Besides gut and adipose tissue, several investigations suggest that pancreas and liver are also target organs for gut microbe during IF (Cheng et al., 2017; Jordan et al., 2019). It is well-known that the forming of T2D needs a long-term course and the pancreatic dysfunction plays a vital role in it (Dor and Glaser, 2013). Therefore, numerous pancreatic studies regarding the prevention of energy dysmetabolism are performed by T2D animal models, such as *db*/*db* mice (Hagberg et al., 2012; Song et al., 2014). Of interest, a diet/drugs-induced model is used to detect the impact of intervention strategy on insulin sensitivity and glucose metabolism (Cheng et al., 2017; Kojima et al., 2003). Among multiple treatments for alleviating T2D, it is worthy to note that IF has been considered as an effective method through pancreatic pathway (Brandhorst et al., 2015; Cheng et al., 2017). In a significant animal study by Cheng et al. (2017), it was demonstrated that IF was an effective treatment for alleviating pancreatic illness in type 1 diabetes (T1D, streptoaotocin-induced) and T2D (*db*/*db* mice). IF was able to increase insulin sensitivity through inhibiting inflammation-induced β-cells failure at late-stage T2D (Cheng et al., 2017). Insulin resistance leads to lower insulin consumption, the decreased production further contributes to the degeneration of β-cells, resulting in T2D by absolute deficiency of insulin (Dor and Glaser, 2013). Cheng et al. (2017) indicated that IF could reverse β-cells depletion and promote their generation via increasing neurogenin 3 (Ngn3) expression. Moreover, IF has also been shown to regenerate human Ngn3-triggered β-cells from T1D subjects via reducing protein kinase A or mammalian target of rapamycin pathway, suggesting that IF-mediated improvements on pancreas may be conservative (Cheng et al., 2017). Finally, an IF regime, implemented in parent mice with diabetes, resulted in progeny that were diabetes-free, which was a highlight in this research (Cheng et al., 2017).

Based on solid evidence that IF-mediated metabolic remodeling, the introduction of research about gut microbiota is predictable. Although there is little published data at present, limited data suggest that gut microbiota has a strong association with pancreatic energy metabolism under IF treatment (Wei et al., 2018a). In 2 in vivo studies from the same research team, Wei et al. (2018a) detected the shaping of gut microbiota while demonstrating the effects of IF on β-cells in *db*/*db* mice, respectively. The results showed that dietary intervention deeply restructured the gut microbial community Wei et al. (2018a). However, the changed genera did not reveal an overlap, suggesting that the differences of protocols may have been more influential on intestinal microbiome than IF-mediated effects Wei et al. (2018a). So, it is a source of regret that in-depth research on gut microbiota-involved regulatory mechanism has not yet been carried out.

Additionally, fasting-induced hepatic transcriptional reprogramming contributes to glucose and ketone production, which is vital for energy supply in mammals (Goldstein et al., 2017). Among multiple transcriptional factors, glucocorticoid receptor (GR)-derived gluconeogenic module, via increasing the expression of cyclic adenosine monophosphate responsive element binding protein 1, and ketone module, via triggering peroxisome proliferator activated receptor alpha activation, construct a complex network of hepatic energy metabolism during fasting (Goldstein et al., 2017). A recent study by Ballegeer et al. (2018) was instructive on the interaction between gut microbiota and GR, although it paid little attention to host energy metabolism and focused on mouse intestine. Thus, it is unknown whether fasting microbial signaling delivers to liver via hepatic GR. However, not all IF strategies have been shown to have the same benefit for host physiology. For instance, in a previously mentioned investigation, Wei et al. (2018a) found that intermittent administration with absent leucine maintained the physiological function of the pancreas islet while it increased the hepatic lipid accumulation and changed body composition. Although the constructed mice model is based on the classical method and the experimental evidence is comprehensive, these positive results have never totally reflected what the phenotypes display in humans (Bowyer et al., 2018; Beli et al., 2018). For example, there are still significant differences in gut microbiota between murine and humans (Bowyer et al., 2018; Beli et al., 2018). Thus, an important target for future research will be the integrative analysis of intestinal microbiota between humans and model animals to determine if this phenotype is common to various species.

3.4. The impact of gut microbiota on IF-mediated improvement of energy metabolism via gut–brain axis

Although the underlying causes of obesity and relative metabolic syndrome are multifactorial, dysregulations of the gut–brain axis are characterized as a central factor (Gupta et al., 2020). In mammals, intestinal and central homeostatic balance contribute to coordinating feeding behavior and energy metabolism, which are influenced by both of dietary quality and feeding rhythmicity (Gupta et al., 2020). Currently, increasing studies indicate that the shaped pattern of gut microbiome by IF treatment is the cause of the improvement of enteric homeostasis, while it also maintains the bio-function of CNS, especially the brain (Cignarella et al., 2018; Gupta et al., 2020; Liu et al., 2020; Zhou et al., 2019). Since there are many biological barriers (such as the blood–brain barrier) and long transmission distance within the gut–brain axis, the shaped pattern of gut microbiome may not directly regulate the brain physiology, but act through its metabolites (Hotamisligil, 2006; Sonnenburg et al., 2016). For instance, intestinal enteroendocrine and enterochromaffin cells can sense the change of the pattern of microbial short-chain fatty acids and then send regulatory signals to the brain via afferent nerves or the circulatory system (Sonnenburg et al., 2016). Thus, aside from peripheral tissues/organs, the contributions of the brain on IF-mediated improvement of energy metabolism should be another concern for the gut microbiota.

The IF-shaped pattern of the gut microbiome has attracted attention due to its close association with the alleviation of energy metabolic disorder and relative neurogenic diseases (Gupta et al., 2020; Zhang et al., 2017, 2018). Compared to obese individuals, IF treatment appeared to result in the alteration of microbial metabolite production, circadian epigenetic and transcriptional landscape of the brain, leading to an anorectic effect in a high fat diet (Racz et al., 2018).

In addition to controlling appetite, gut microbiota is also strongly involved in alleviating energy dysmetabolism-triggered neurodegenerative diseases (Liu et al., 2020). Cognitive decline is one of the neurodegenerative diseases which is identified as a complication of T2D and characterized by brain insulin resistance, cerebral microvascular damage, neurotransmitter metabolism disturbance, mitochondrial dysfunction, and neuroinflammation (Carvalho et al., 2015; De Felice and Ferreira, 2014; Gold et al., 2007). The homeostasis of the microbial community and metabolites, including short chain fat acids (SCFA), secondary bile acids, and serotonin, is essential for maintaining cognitive functions via modulating the permeability of the blood–brain barrier, energy homeostasis, and synaptic transmission (Braniste et al., 2014; Diaz Heijtz et al., 2011; Filipe De Vadder et al., 2014). A recent investigation supported this viewpoint and demonstrated gut microbiota-derived metabolites as a novel therapeutic strategy against T2D-induced cognitive disorder (Liu et al., 2020). In this study, Liu et al. (2020) reported that to IF re-structured the pattern of the gut microbiome and its metabolites in mice with T2D-triggered cognitive dysfunction, resulting in an improvement of behavioral impairment. However, antibiotics-mediated microbiota depletion partly abolished the neuroprotective effects under IF treatment (Liu et al., 2020). Moreover, the similar positive results were also observed in diabetic mice with microbial metabolites supplementation (including 3-indolepropionic acid, serotonin, SCFA or tauroursodeoxycholic acid) which have been found to have high expression in the gut from IF treatment, suggesting that the microbiota–metabolites–brain axis is responsible for regulating the brain physiology under an IF condition (Liu et al., 2020).

Also, MS is a CNS inflammatory demyelinating disease that is affected by dietary habits (Cignarella et al., 2018). In other words, energy dysmetabolism-induced obesity is a risk factor for MS epidemiology (Ascherio, 2013). Recently, IF has similarly been documented to ameliorate MS via shaping the gut microbiome, both in clinical cases and in the rodent model (Cignarella et al., 2018). IF-induced pattern of gut microbiome (which was characterized as a higher bacterial abundance and enrichment of the Lactobacillaceae, *Bacterioidaceae* and Prevotellaceae families) activated anti-oxidative pathways (including ketone formation and glutathione metabolism) (Cignarella et al., 2018). Moreover, IF directly targeted T cells to increase the number of regulatory T cells and to decrease Interleukin-17 producing T cells (Cignarella et al., 2018). Notably, FMT assays further determined that IF-mediated immunomodulatory effects on MS mice were at least partially dependent on gut microbiota, supporting that gut microbiota serves as a key link between dietary habits and CNS (Cignarella et al., 2018).

In addition to MS, Parkinson's disease (PD) has also been found to be strongly associated with dietary habits (Zhou et al., 2019). IF administration has been reported to attenuate the loss of dopaminergic neurons in the substantia nigra and accelerate the retention of motor function by increasing the expression level of brain-derived neurotrophic factor in a rodent model (Zhou et al., 2019). During IF-mediated neuroprotection, FMT test has once again proven gut microbiota to be responsible for IF alleviating PD (Zhou et al., 2019). Separately, an IF-shaped pattern of gut microbiome, indicated in the improvement of PD, is characterized as having a higher abundance of *Firmicutes*, *Tenericutes*, and *Opisthokonta* and lower abundance of *Proteobacteria* (Zhou et al., 2019).

In summary, gut microbiota, as an important manipulator, appear to be an essential link among host peripheral tissues/organs, CNS and global energy metabolism under IF treatment. Emerging reports have gradually improved our understanding by providing interesting regulatory pathways and perspectives (Table 1). Despite these findings, many unknowns still exist regarding the mechanism of action, thus requiring further research.

4. A potentially recommendatory strain based on the observational data for IF-mediated alternated pattern of gut microbiota

As a well-known observation in clinical cases and rodent models, the greatest abundance of microbial phyla in the gut is classified as Bacteroidetes and Firmicutes (Beli et al., 2018). Moreover, this phenotype not only limited to mammalian, reptile (*Burmese pythons*) and fish (*Carassius auratus*) have also been reported with these as their dominant status (Costello et al., 2010; Li et al., 2019). As mentioned previously, large differences of influenced microbial structures exist among relevant studies (Table 2). By simply summarizing statistics, it becomes appearent that 2 major phyla, *Bacteroidetes* and *Firmicutes*, are both significantly affected by IF. However, contradictory findings regarding these 2 phyla contribute to rarely determining or explaining their regulatory mechanism. Thus, the analysis of the fasting microbiome has gradually turned to focus on minor ethnicities which have been shown to be obviously affected by IF.

Interestingly, when the regularity of daily dietary input is shaped, the abundance of Verrucomicrobia phylum are shown to be increased, whereas Proteobacteria and Actinobacteria are reduced (Table 2). In Verrucomicrobia phylum, *A. muciniphila* is a mucin-degrading Gram-negative bacteria which was isolated from the host intestinal mucus layer (Ansaldo et al., 2019). In healthy individuals, such symbionts account for 3% to 5% of the total microbial community, but in patients with obesity and murine models, the abundance is significantly reduced, suggesting that relative abundance is negatively correlated with host obesity (Belzer and de Vos, 2012; Everard et al., 2013; Mithieux, 2018). Clinical research indicates that the abundance of *A. muciniphila* is decreased in various pathological situations, including diabetes and fatty liver (Grander

Table 1
Multiple gut microbiota-involved regulatory pathways under intermittent fasting (IF) treatment.

Animal	Physical location	Signaling pathway	Function	References
Mice	Brain	Gut microbiota—Short chain fat acids—Brain; Gut microbiota—Secondary bile acids—Brain; Gut microbiota—3-Indolepropionic acid—Brain; Gut microbiota—Serotonin—Brain; Gut microbiota—Ketone and Glutathione —Central nervous system; Gut microbiota—Brain-derived neurotrophic factor—Central nervous system	Regulation of feeding behavior; alleviation of cognitive decline, multiple sclerosis, and Parkinson's disease	Sonnenburg et al. (2016); Racz et al. (2018); Liu et al. (2020); Zhou et al. (2019)
Mice	Liver	GR—CREB1—PPARγ	Increase of glucose and ketone production	Goldstein et al. (2017); Kinouchi et al. (2018b)
Mice/Human	Pancreas	PKA/mTOR—Sox2/Ngn3	Recovery of insulin secretion by β cells	Wei et al. (2018a, 2018b); Cheng et al. (2017)
Mice	Adipose tissue	CLK2—CREBP—UCP1; IF—VEGF—M2 macrophage	Increase of BAT thermogenesis; promotion of WAT browning	Li et al. (2017); Kim et al. (2017); Hatting et al. (2017)
Mice/Fly	Intestine	Lactobacillus—T cells	Increase of intestinal barrier; alleviation of intestinal inflammation;	Catterson et al. (2018); Rangan et al. (2019)

GR = glucocorticoid receptor; CREB1 = cyclic AMP response element binding protein 1; PPARγ = peroxisome proliferators-activated receptor γ; PKA = protein kinase A; mTOR = mammalian target of rapamycin; Sox2 = SRY (sex determining region Y)-box 2; Ngn3 = neurogenin 3; CLK2 = CDC-like kinase 2; CREB1 = cyclic AMP response element binding protein 1; PPARα = peroxisome proliferators-activated receptor α; CREBP = cyclic AMP response element binding protein; UCP1 = ncoupling protein 1; VEGF = vascular endothelial growth factor; BAT = brown adipose tissue; WAT = white adipose tissue.

Table 2
Intermittent fasting (IF)-mediated influence on gut microbial community in rodent model (Phyla).

Phyla		Relative abundance		References
		Increase	Decrease	
Mice	Bacteroidetes	2	3	Li et al. (2017); Cignarella et al. (2018); Zarrinpar et al. (2014); Wei et al. (2018a); Beli et al. (2018); Liu et al. (2020); Guo et al. (2020); Zhang et al. (2020)
	Firmicutes	4	2	
	Proteobacteria	0	2	
	Verrucomicrobia	3	0	
	Actinobacteria	0	2	

et al., 2018; Plovier et al., 2017). Further studies showed that its abundance has a negative correlation with adipose inflammation, hyperlipidemia, and hyperglycemia (Depommier et al., 2019; Schneeberger et al., 2015; Shen et al., 2016). Furthermore, *A. muciniphila* has also been demonstrated to enhance host intestinal barrier function (Belzer and de Vos, 2012; Chelakkot et al., 2018).

As a new probiotic, *A. muciniphila* is indeed a potential therapeutic agent of obesity since its isolation and identification (Ansaldo et al., 2019). Supplementation of *A. muciniphila* can balance fat distribution, improve metabolic endotoxemia-induced inflammation and ultimately restore the gut barrier (Reunanen et al., 2015). Surprisingly, thermal extermination by auto clavation dose not eliminate *A. muciniphila*-induced improvements, but rather seemed to enhance its positive effects, suggesting that this particular probiotic may be slightly different and requires further study (Plovier et al., 2017). Recently, Amuc_1100, a specific outer membrane protein of *A. muciniphila*, has been identified as a key signaling molecule for activating host immunity through the toll-like receptor 2 pathway within the intestinal epithelium (Ottman et al., 2016). Notably, the abundance of *A. muciniphila*, the above-mentioned strain that is negatively correlated with obesity and related metabolic syndrome, has shown to be increased by IF administration (Table 2).

To sum up, these data indicate that *A. muciniphila* may serve as a positive factor in IF-mediated alleviation of energy dysmetabolism. There is an extensive application prospect of *A. muciniphila-derived* metabolites and relative therapeutic strategies in the prevention and treatment of obesity and T2D.

5. Circadian rhythm—a hopefully regulatory pathway for gut microbiota in IF-involved improvement on energy metabolism

Most mammals have evolutionarily developed endogenous rhythms to ensure that various organs/tissues optimally exert/harmonize anabolic vs. catabolic functions during the day—night cycle (Wang et al., 2017). This specific physiological phenomenonis beneficial to save energy upon food scarcity and release energy during an active phase (Panda et al., 2002). In contrast to the master biological clock located in the suprachiasmatic nucleus of the hypothalamus, many peripheral organs/tissues also have their own similar rhythmic oscillators (Gabriel and Zierath, 2019; Liu et al., 2017, 2018; Sato et al., 2017; Stenvers et al., 2019; Wang et al., 2017). In Table 3, we reviewed multiple circadian rhythmic transcriptional factors-mediated various metabolisms in peripheral tissues over past 4 years. These studies show that the circadian rhythms of numerous peripheral tissues are responsible for regional/systematic energy metabolism by direct/indirect pathways.

As dominant timing influence factors, feeding and fasting behavior appear to be an important cue to link these mechanisms (Gill and Panda, 2017). By including samples from both clinical research and model animals, the existence of an association between IF and intrinsic circadian rhythm has been reported (Gill and Panda, 2017; Sutton et al., 2018). To better coordinate intrinsic metabolic rhythm, the timing of feeding and fasting has been continually improved by numerous investigations, which is able to optimize the energy metabolism at the molecular level (Hatori et al., 2012; Scheer et al., 2009). Unlike time-restricted feeding, alternate-day fasting has been rarely proposed as fasting timeliness in previous research (Sutton et al., 2018). However, Kinouchi et al. (2018a) indicated that fasting enabled the triggering of the temporal circadian rhythmicity gene expressional switch and maintained this phenotype during the whole stage until refeeding, suggesting that timeliness might be another control node for IF-mediated energy optimization.

Table 3
Multiple circadian rhythmic transcriptional factors-mediated metabolisms in peripheral tissues.

Animal	Physical location	Function		References
		Key regulatory pathway	Metabolism	
Mice	Skeletal muscle	1. Bmal1—HIF1α; 2. Rev-erb—HDAC3; 3. CRY1/2—PPARδ; 4. Bmal1—Dgat2, Rev-erbα—MuRF-1, Atrogin-1	1. Circadianaffects metabolic adaptation to hypoxia via HIF1α pathway; 2. circadian cues is responsible for muscle fuel metabolism through HDAC3 transcriptional regulation; 3. CRY1/2 alters energy storage and energy production; 4. the promotionof neutral lipid storage during diurnal cycles and the coordination of lipid and protein catabolism	Bien Peek et al. (2017); Hong et al. (2017); Jordan et al. (2017); Dyar et al. (2018)
	Liver	1. Rev-erbα—HNF4A/HNF6; 2. CO—Clock/Bmal1; 3. NAD^+—SIRT1—Acetyl-CoA; 4. ER stress—CPEB4-mediated UPR activity; 5. Bmal1—ASS1; 6. Bmal1—ChREBP; 7. Bmal1—METTL3—PPARα; 8. HNF4A—Bmal1	1. Glucocorticoid receptor recruitment and segregation of carbohydrate and lipid metabolism; 2. the regulation of glucosemetabolism; 3. circadian clock regulates live metabolism and aging; 4. circadian-depended CPEB4 protect liver from hepatic steatosis; 5. Clock modulatesarginine biosynthesis; 6. BMAL1 induces de novo lipogenesis viacouplingChREBP; 7. circadian clock regulates live metabolism via controllingm6A mRNA methylation	Chaix et al. (2019); Sato et al. (2017); Klemz et al. (2017); Caratti et al. (2018); Maillo et al. (2017); Krishnaiah et al. (2017); Lin et al. (2017); Zhang et al. (2018); Toledo et al. (2018); Guan et al. (2018); Zhong et al. (2018); Qu et al. (2018)
	Intestine	1. LPS—TLR4—IL23, IL-22—STAT3—Rev-erbα—NFIL3; 2. PPARα-dependent transcriptional reprogramming	1. circadianaffects lipid uptake of intestinal enterocytes; 2. tissue-specificrhythmic PPARα regulates energy metabolism.	Wang et al. (2017); Mao et al. (2018); Tognini et al. (2017)
	Adipose tissue	1. Clock—HDAC3—c-Myc; 2. Bmal1—angiotensinogen	1. Circadianregulates proliferation of adipose tissue; 2. the regulation of blood pressure	Chang et al. (2018); Liu et al. (2017)
Humans	Skeletal muscle	1. PPAR pathway; 2. Clock	1. Circadian misalignment reduces insulin sensitivity; 2. circadian misalignment damage normalglucolipid metabolism	Perrin et al. (2018); Wefers et al. (2018)
	Adipose tissue	1. Per2; 2. Signal pathways associated with lipid metabolism, cell differentiation, and DNA damage	1. Circadian rhythm disorders alters the level of plasma glucose; 2. acute sleep loss results in tissue-specific DNA methylationandtranscriptomic changes	Cedernaes et al. (2018); Wehrens et al. (2017)

Bmal1 = aryl hydrocarbon receptor nuclear translocator-like protein 1; HIF1α = hypoxia-inducible factor-1α; HDAC3 = histone deacetylase 3; CRY1/2 = cryptochromes1/2; PPAR = peroxisome proliferator-activated receptor; Dgat2 = diacylglycerol O-acyltransferase 2; MuRF-1 = muscle RING finger 1; HNF4A/HNF6 = hepatocyte nuclear factor 4 alpha/6; NAD^+ = oxidized nicotinamide adenine dinucleotide; Acetyl-CoA = acetyl coenzyme A; ER = endoplasmic reticulum; CPEB4 = cytoplasmic polyadenylation element binding protein4; UPR = unfolded protein response; ASS1 = argininosuccinatesynthetase 1; ChREBP = carbohydrate-responsive element-binding protein; METTL3 = N6-adenosine-methyltransferase 70 kDa subunit; IL = interleukin; Per2 = period circadian regulator 2.

In mammalian gastrointestinal tract, gut microbiota also has its own circadian variation (Thaiss et al., 2016). On the basis of symbiotic relationship, there are strong associations between gut microbiota and host. Therefore, the hypothesis has been proposed that microbial circadian rhythm triggered host metabolic changes. Interestingly, Thaiss et al. (2016) proved this hypothesis through integrated multi-omics analysis and found that along with gut microbial diurnal oscillations, the transcriptome related to the circadian rhythm of mice also changes at multiple tissues/organs level, whereas these gut microbiota-derived host metabolic oscillations were significantly damaged in mice with broad-spectrum antibiotics treatment (Thaiss et al., 2016). Based on the mouse model, another study also observed that antibiotics-mediated depletion of gut microbiota was responsible for reducing the transcriptional level of Aryl hydrocarbon receptor nuclear translocator-like protein 1 (*Bmal1*) and Cryptochromes1 (*Cry1*), which indicated that the core of the clock mechanism was damaged, resulting in glucose and lipid dysmetabolism (Mukherji et al., 2013). Similar results were also detected in the skeletal muscle (Wu et al., 2019).

Further studies reveal that microbial metabolites are involved in regulating host circadian rhythm. SCFA and their derivatives have been documented to modulate period circadian regulator 2 (Per2) and Bmal1 genes in the host peripheral and central clock mechanism under IF treatment (Ku et al., 2020). An important investigation by Wang et al. (2017) demonstrated evidence for gut microbiota modulating host lipid uptake via shaping the expression of the rhythm factor (*REV-Rerbα)* in intestinal epithelial cells. In this study, gut microbial functions surrounding circadian rhythm, metabolites (especially Lipopolysaccharide), transcriptional regulation and lipometanolism in jet-lag mouse models were performed and demonstrated a key pathway, gut microbial metabolites-REV-Rerbα-Nuclear factor, interleukin 3 regulated, in enterocytes (Wang et al., 2017). At present, a majority view claims that the modulations originating from gut microbiota during the dark phase include repair of DNA damage, cell development, and energy metabolism, whereas the light phase showed more pathways regarding “maintenance”: detoxification, motility and environmental sensing (Thaiss et al., 2014).

Overall, these data indicate that diurnal activities of intestinal microbiota and its metabolites are responsible for remodeling host metabolic patterns during IF treatment. Considering the published mechanism of gut microbiome on host energy metabolism during IF, the hypothesis of circadian rhythmic modulation may be considered as a prime pathway. Due to there are many limitations on clinical

research, recent reports are evidenced via the mouse model (Fig. 1). But, once the scope of linkage can be established, the more commonality and universality will be revealed, which will further contribute to developing novel strategies for treating obesity and relative metabolic syndromes (Anafi et al., 2017).

6. Limitations of current studies on the effects of gut microbiota during IF

A limitation common to this field is the lack of a gut microbiota-mediated integrity mechanism. Admittedly, bulk data of gut microbiota-seq provide many discernible differences between various treatments, but the complex microbial structure and metabolic composition cannot clearly determine the details of the regulatory circuit and restrict further research (Qi and Han, 2018; Wang et al., 2017). However, specific microbiota-mediated functional analysis has been gradually developed to thoroughly investigate the mechanism (Maria Carlota Dao et al., 2016; Wang et al., 2017). This procedure will lead to a novel field for gut microbial research and contribute to developing future therapeutic interventions for treating jet-lag and obesity. It is expected that the analysis of a single strain will reveal more important evidence to illustrate the role of gut microbiota in IF-mediated energy control.

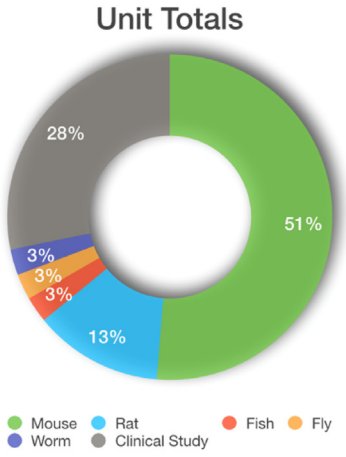
Another issue pertaining to IF is how to create a series of procedures for transition from animal models to clinical research. We have found 39 typical reports published in the past 4 years, of which only 11 articles are involved in clinical studies, indicating that this corresponds to about 1/4 of the total research (Fig. 1). In these investigations, the rodent model alone makes up about 60% of unit totals, while other animal models, including fly, worm, and fish, only exist in a few studies (Fig. 1). Moreover, the research associated with gut microbiota in this field is still in its the initial stages, suggesting that there are more valuable regulatory pathways that deserve further study (Fig. 1).

Finally, the sorting protocol of the duration of fasting has been rarely reported. Among various shackles, the biggest issue is that there is not a robust standard to classify its development phase. Owing to huge variations of requirements drive the alternation of optimal courses of treatment in different experimental procedures, it will likely make more efforts to construct a complete research system. However, the accurate pattern of gut microbiome for each individual protocol is not yet prospected and sketched in accordance with existing tables due to individual differences and a lack of data. Based on the continuous improvement of methodologies for detecting gut microbiota abundances and functions, a dizzying array of analyzed data on these symbionts may provide an answer whether it will develop an effective strategy to solve the problem (Abu-Ali et al., 2018; Caporaso et al., 2010; Claesson et al., 2010; Kanehisa et al., 2012; Kerkhof et al., 2017; Langille et al., 2013; Weinstock, 2012).

7. Prospective

Now is an exciting time for microbiologists (Fig. 2). The research about the effects of a single strain on a host is gradually replacing large-scale microbiome analysis and thus reveals a novel canto to

SUBJECT		NUMBER	REFERENCES
Animal Model	Mouse	20	Supplementary Materials
	Rat	5	
	Fish	1	
	Fly	1	
	Worm	1	
Clinical Study		11	
UNIT TOTALS		39	



CORRELATION	NUMBER	REFERENCES
Gut Microbiota	8	Supplementary Materials
Others	31	
UNIT TOTALS	39	

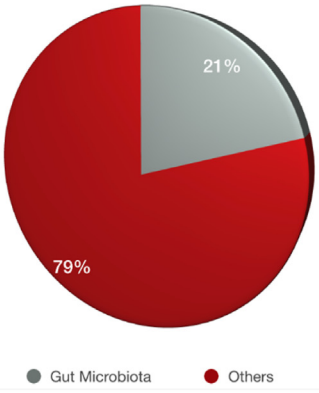


Fig. 1. Typical reports about IF over past 4 year. Upper table and pie chart display the typical reports about IF among various sets of experimental modes during past 4 years. Following diagram shows the percentage of studies regarding gut microbiota in these reports.

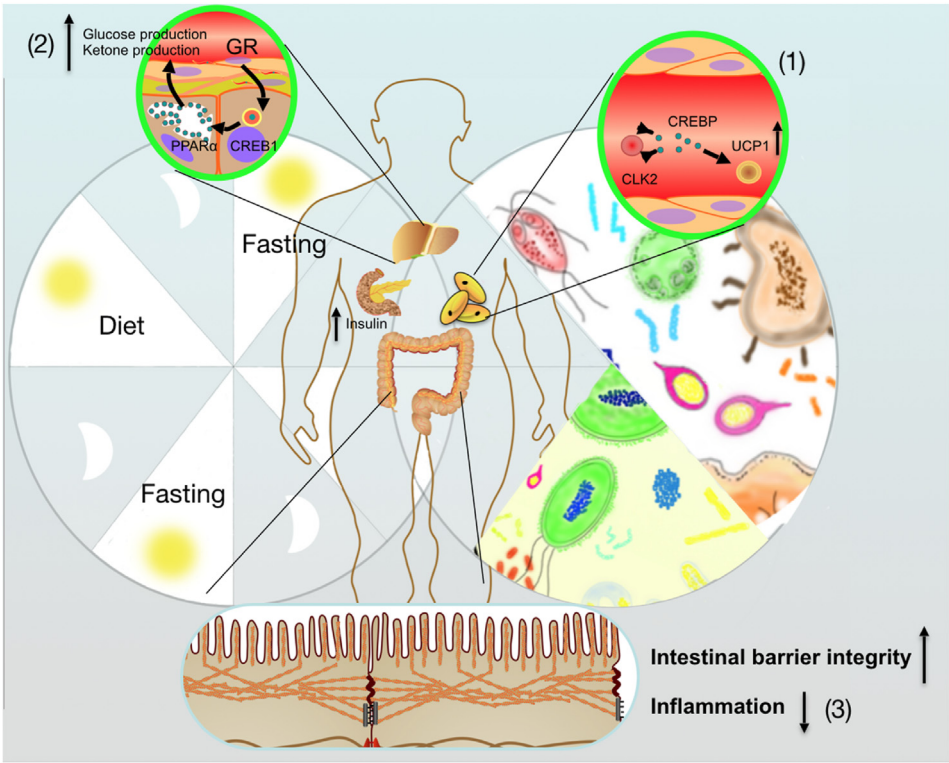


Fig. 2. A summary of IF-mediated positive effects by which gut microbiota regulates host energy metabolism. (1) By improving gut microbial ecosystem, IF promotes WAT beiging (Li et al., 2017). (2) Gut microbiota involves in increasing hepatic ketone production during periods of nutrient deprivation (Crawford et al., 2009). (3) Optimized microbial community by IF is also responsible for the protection of host intestinal barrier. GR = glucocorticoid receptor; CREB1 = cyclic AMP response element binding protein 1; PPARα = peroxisome proliferators-activated receptor α; CREBP = cyclic AMP response element binding protein; UCP1 = ncoupling protein 1; CLK2 = CDC-like kinase 2.

further detect gut microbiota-mediated positive influences upon IF conditions (Maria Carlota Dao et al., 2016; Wang et al., 2017). Based on numerous achievements from previous studies and increasingly developing technologies, it is reasonable to believe that these issues will be finally determined (Fig. 2). With more conclusions linking gut microbiota and host energy metabolism, and revealing the role of intestinal bacterial in IF-modulated energy optimization, these kinds of symbionts will greatly refurbish our understanding and contribute to improving drug development for obesity, diabetes, and related metabolic syndromes.

Author contributions

Chao Sun and **Bohan Rong** designed this paper. **Bohan Rong**, and **Qiong Wu** collected the references. **Bohan Rong** and **Muhammad Saeed** were responsible for the manuscript writing.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and 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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