Review

Non-Coding RNAs and Gut Microbiota Might Be Involved in the Pathogenesis of Cardiac Arrhythmias

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Review

Non-Coding RNAs and Gut Microbiota Might Be Involved in the Pathogenesis of Cardiac Arrhythmias

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Abstract: The non-coding RNAs (ncRNAs) are indispensable for controlling genes and genetic programming during development, as well as for health and cardiovascular diseases. Cardiac arrhythmia is a frequent cardiovascular disease, which has a complex pathology. Recent studies have shown that ncRNAs are also associated with cardiac arrhythmias. Many non-coding RNAs and/or genomes have been reported as a genetic background for cardiac arrhythmias. Arrhythmias may be affected by several functional and structural changes in the myocardium. Therefore, ncRNAs might be indispensable regulators of gene expression in cardiomyocytes, which could play a dynamic role in regulating the stability of cardiac conduction and/or in the remodeling process. Although it remains almost unclear how ncRNAs regulate the expression of molecules for controlling the cardiac conduction and/or in the remodeling process, gut microbiota and immune system within the intricate networks might be involved in the regulatory mechanisms. This study would discuss them and provide a research basis for ncRNAs modulation, which might support the development of emerging innovative therapies against cardiac arrhythmias.

Keywords: ncRNA; lncRNA; miRNA; cardiac arrhythmia; atrial fibrillation; gut microbiota; APRO family protein

1. Introduction

Cardiac arrhythmias are a set of heterogenic dysfunctions in the heart rhythm, which may be often defined as any variations in the rate of the normal heart. Abnormal impulse formations and disturbances in conduction may be two major reasons responsible for arrhythmias. However, the physiological dysfunctions linked to the specific arrhythmias are very intricate. The primary pace-making activity of the heart is determined by a spontaneous action potential within atrial node cells [1]. At present, it has been suggested that the distinctive pace generation might characteristically rely on probable membrane clock mechanism. The membrane clock consists of plasma membrane ion channels carrying an inward current [2]. Therefore, the rhythm-associated ion channels implicated in the initiation or progression of the action potential have been well documented. Most likely, arrhythmias are mainly caused by imbalances of these calcium ion channels and dysregulations of conduction in cardiac muscles. The identification of genetic components underlying the cardiac arrhythmias have also highlighted the specific role of ion channels. Most ion channels are protein complexes that are positioned in the cardiomyocyte sarcolemma, and they might play a role in calcium ion flow conduction [3].

Non-coding RNAs (ncRNAs) have been shown to regulate a variety of ion channels and/or intercellular linking proteins/molecules, suggesting that ncRNA may be an important regulator of cardiovascular diseases [4]. Therefore, we deliberate recent findings on the implication of ncRNAs in the development of the most common forms of arrhythmias with a focus on therapeutic and/or clinical application. In recent years, it has been revealed that ncRNA could regulate disease

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development [5]. The ncRNAs are around 200-nt base sequences that might regulate the genetic, epigenetic gene expression as well as intra-cellular signaling mechanisms [6]. In general, the ncRNAs have been used as biomarkers for diagnosis and/or treatment due to their involvement in the disease commencement. Hence, ncRNA has been also investigated in cardiovascular diseases [7]. **(Figure 1)** The ncRNAs have enormous importance in clinical applications, which are usually categorized into several categories such as miRNAs, circRNAs, and/or lncRNAs [8]. Recent studies have shown that the association between lncRNAs and protein may be related to the cardiac arrhythmias. Short interference RNA (siRNA) could be often used to target the specific ncRNA. RNAi-mediated siRNAs are highly adjustable, which could be used to suppress their mRNA's encoding protein. The miRNAs are approximately 22-nucleotide RNA molecules that could regulate cell signaling and/or decrease the expression of specific genes by modifying the translation procedure [9].

Although more than a few arrhythmogenic mechanisms such as alterations in calcium ion channels function and/or oxidative stresses in cardiac cells have been widely studied, there are still some vacancies to be clarified. Somewhat, the understanding of pathogenesis for the prevention and/or treatment of cardiac arrhythmias without any side effects has become an important issue to be solved urgently. In this regards, the gut microbiota might have a significant impact on cardiac arrhythmias through a variety of mechanisms, suggesting a broad range of conceivable treatment options [10]. In addition, a related study suggest that cardiac arrhythmias may associate with nutrient intake and/or some metabolisms [11]. The exploration of the related mechanisms of dysbiosis of the gut microbiota including the increase of harmful metabolites has been increasingly discovered. On this basis, it has been shown that abnormal metabolites of gut dysbiosis might be linked to cardiac arrhythmias [12]. Here, a comprehensive arrhythmogenicity study have been briefly summarized, which might provide theoretical basis for novel treatment strategies inspiring the prevention and/or treatment of cardiac arrhythmias.

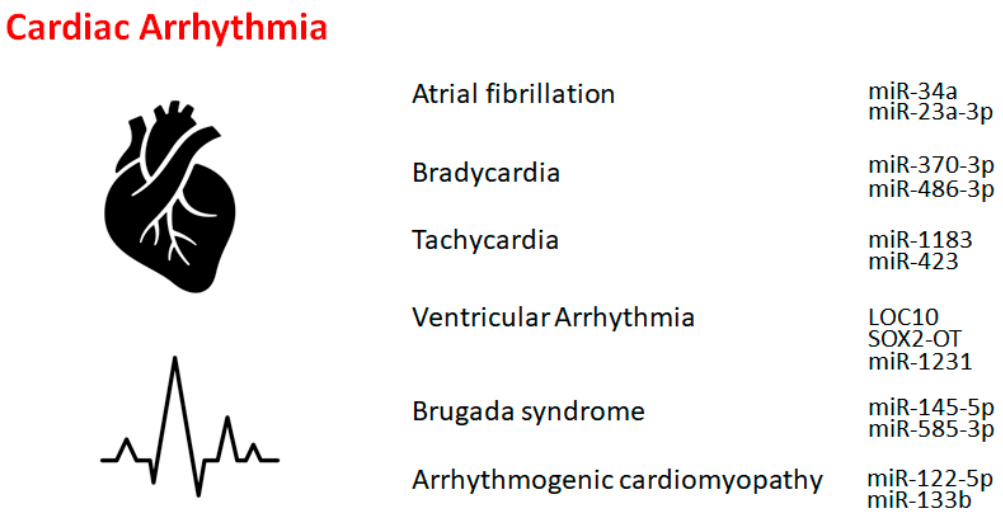

Figure 1. Schematic representation of the players of ncRNAs involved in the cardiac arrhythmias. Example ncRNA molecules are shown for each cardiac arrhythmia.

2. Atrial Fibrillation

Atrial fibrillation is an asymmetrical heart rhythm, which might commonly lead to heart palpitations. Interestingly, individuals carrying the non-coding 4q25 locus near the *PITX2* gene were 60% more susceptible to this abnormal heart rhythm [*13*]. Similarly, lncRNAs may be potentially associated with the development of Atrial fibrillation. Several lncRNAs including *LINC00844, RP11-532N4.2, UNC5B-AS1, RP3-332B22.1, RP11-432J24.5, and RP11-557H15.4* have been shown to be differentially expressed in patients of atrial fibrillation compared to normal individuals, whose target might be related to the calcium signaling pathway and/or toll-like receptor signaling pathway [14,

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15]. In addition, several miRNAs including *miR-135a* might be involved in the process of atrial fibrillation.

Atrial fibrillation is the most prevalent type of arrhythmia worldwide [*16*]. Atrial fibrosis is a hallmark feature of atrial structural remodeling in atrial fibrillation, which is regulated by the TGF-*β*1/Smad3 pathway. The dysregulation of tissue blockers of matrix metalloproteinases including MMPs and TIMPs linked to collagen upregulation is also a key factor in the development of atrial fibrillation. The *miR-146b-5p* might be an inhibitor of TIMPs protein expression, which may be increased in atrial tissue with atrial fibrillation. Furthermore, some profibrotic markers, such as MMP9, TGFβ1, and COL1A1, were downregulated upon *miR-146b-5p* knockdown, whereas TIMP4 caused inversed expression patterns [17]. Another mechanism underlying atrial fibrillation is ferroptosis, which is defined as iron-dependent cell death due to excessive accumulation of peroxidized polyunsaturated fatty acids. Interestingly, the occurrence of ferroptosis in atrial fibrillation has been shown to be promoted by *miR-23a-3p*. In addition, *SLC7A11* is a direct target of *miR-23a-3p*, which might be also associated with ferroptosis [18]. Alternative miR-dependent gene regulation could elicit the initiation and progression of atrial fibrillation. For example, *miR-34a* could upregulate the expression of tandem of P domains in a fragile inner repairing K+ channel-linked acid-sensitive K+ channel 1 (TASK-1), which might promote a reduction in the resting membrane potential [19].

3. Bradycardia and Tachycardia

Bradycardia is a heart dysfunction described by a decreased heart rate mostly lower than 50 beats/min. The main etiological factors of bradycardia may include the dysregulation of sinus, atrial or junctional bradycardia, and/or an intricate transmission system with atrioventricular block. The most frequent form of bradycardia asymptomatically takes place during sleep and/or in athletes [20]. Bradycardia is usually regulated by a range of molecules including ncRNAs at a molecular levels. Transcription factors also control the expression of genes involved in BA by modulating a variety of effectors including miRNAs. For example, it has been demonstrated that the function of *miR-370-3p* could contribute to the development of bradycardia [21], which might be triggered via the reduced function of sinus node pacemaker channels with a related reduction of the ionic current. The *miR-370-3p* could directly bind to the mRNA of HCN4 to suppress the activity of HCN4 [21]. Similarly, the *miR-486-3p* could suppress the HCN4 inducing a sinus node dysregulation such as bradycardia [22, 23]. Supraventricular arrhythmia is an example of tachycardia that starts in the upper compartments of the heart.Tachycardia is known to be considered as a fast heartbeat, which might be also regulated by a range of molecules including ncRNAs at a molecular levels. For example, the expression of *miR-1183* may be considerably upregulated in tachycardia. Elevated expression of *miR-1183* might serve as a tissue biomarker for atrial remodeling, which might be of potential significance in cardiac disease [24]. Similarly, transcriptomic data from the urine sample have revealed significantly reduced levels of miRNAs including *miR-423, miR-1180, miR-3162, miR-319,7 miR-3613, miR-6511, miR-6763.* The changes in these miRs were associated with increased expression of profibrotic markers, such as Col I, Col III, fibronectin, and TGF-β. *MiR-423* specifically was shown to regulate calcium-handling proteins, such as the phosphorylated calmodulin-dependent protein kinase II, which might regulate the development of tachycardia [25].

4. Other cardiac rhythm disorders

Ventricular arrhythmias are described as irregular heartbeats that derive from the ventricles. The origin of ventricular arrhythmias might be sympathetic remodeling that originates in myocardial infarction. Various ncRNAs are important regulators of inflammation and sympathetic remodeling following the myocardial infarction. Several lncRNAs are potentially implicated in ventricular arrhythmias following myocardial infarction. For example, the lncRNA *LOC100911717 (LOC10)* might be increased in cardiac cells and macrophages at the infarcted heart area [26]. Another important factor of ventricular arrhythmias may be NLRP3 inflammasomes. It has been demonstrated that the role of *SOX2-OT* lncRNA in regulating NLRP3 inflammasome-mediated

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ventricular arrhythmias. The levels of *SOX2-OT* and NLRP3 inflammasomes could be increased after ventricular arrhythmias [27]. Similarly, the *miR-2355-3p* and *miR-1231* may play key roles in the regulation of ventricular arrhythmias [28, 29].

Long QT and short QT syndrome are known as the entity of Brugada syndrome [30]. Risk stratification for sudden cardiac death in patients with Brugada syndrome remains a major challenge. Brugada patients display a distinct miRNA expression profile compared with unaffected control individuals. For example, the *miR-145-5p* and *miR-585-3p* are associated with the standing position of Brugada patients, which might be the potential utility of leucocyte-derived miRNAs as prognostic biomarkers for Brugada syndrome [31, 32]. Arrhythmogenic cardiomyopathy is a genetically determined disorder caused by mutations in proteins constituting desmosomes, which is an inherited cardiomyopathy histologically characterized by the replacement of myocardium by fibrofatty infiltration, cardiomyocyte loss, and inflammation [33]. Inflammation might be also involved in the pathogenesis of arrhythmogenic cardiomyopathy with various inflammatory cytokines [34]. Consistently, it has been suggested that circulating levels of cytokine receptors (IL1-R1, IL6-R, TNF-R1/R2) may be elevated and associated with the risk of arrhythmias in arrhythmogenic cardiomyopathy [35-37]. In particular, myocardial expression of IL-17 and/or TNF is substantially enhanced in all cases of arrhythmogenic cardiomyopathy [38]. In a large cohort of samples, the *miR-122-5p, miR-133b, miR-133a-3p, miR-142-3p, miR-183-5p* and *miR-182-5p* could possess high diagnostic potential in arrhythmogenic cardiomyopathy patients [39, 40]. The implication of miRNAs in the pathogenesis of arrhythmogenic cardiomyopathy has been the objective of multiple studies.

5. Gut microbiota and cardiac arrhythmia

Disruption of gut microbiota could induce cardiorespiratory morbidity. Consistently, modulation of autonomic homeostasis via the gut microbiota-brain axis could control the heart rate [41]. The adult gut system might be an extremely diverse and dynamic ecosystem [42, 43], which exert specific physiological functions including immune regulation, gut mucosal protection, and conservation of nutritional metabolism in addition to the development of several diseases [44]. Microbiota elements can directly or indirectly trigger vagus nerve afferent fibers through the gut endocrine cells, which could stimulate the central nervous system (CNS). Depending on the substance, the different SCFAs produced by microbiota maybe activate vagal afferent fibers in different ways. For example, butyric acid, a short fatty acid, directly affects afferent terminals [45, 46]. An increase in the concentration of butyric acid at the colon may produce a significant hypotensive effect which depends on the afferent colonic vagus nerve signaling and GPR41/43 receptors [46]. Several studies have investigated the effects of food components on gut microbiota, which could be an imperative target for the forthcoming treatment of arrhythmias through the modification of gut microbiota. For example, patients with arrhythmias may prefer to take further energy from animal fat [47]. Therefore, patients with cardiac arrhythmias are often found with atherosclerosis. In addition, diabetes may be also a frequent co-morbidity in individuals with arrhythmias. Furthermore, the interaction between some drugs and their impact on gut microbiota may result in uncontrolled arrhythmias [*48-50*]. Recent increasing data suggest that regulatory non-coding RNAs such as miRNAs, circular RNAs, and lncRNA may affect host-microbe interactions. These ncRNAs have been also suggested as potential biomarkers in microbiome-associated disorders with a direct cross-talk between microbiome composition and ncRNAs [51]. Epigenetically, *miR-23a-3p* could lead to Th17/Treg imbalance and participate in the progression of Graves' disease [52], which might be also involved in the mechanism underlying atrial fibrillation. Gut microbiota plays a vital role in the pathogenesis both of atrial fibrillation and Graves' disease [52]. The imbalance of Th17/Treg cells induced by the alteration of gut microbiota plays a vital role in the pathogenesis of arrhythmias [53, 54]. Interestingly, altered composition of gut microbiota could change the expression of hepatic *miR-34a* [55], which might be also involved in the development of atrial fibrillation. A negative correlation between *miR-122-5p* and the intestinal bacteria including *Bacteriodes. uniformis* and *Phascolarctobacterium. Faecium* has been revealed, suggesting that the crosstalke between miRNA and gut microbiota could regulate the intracellular signal transduction by controlling key genes [56]. As

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mentioned before, the *miR-122-5p* could possess great diagnostic potential in arrhythmogenic cardiomyopathy patients [40, 57]. **(Figure 2)**

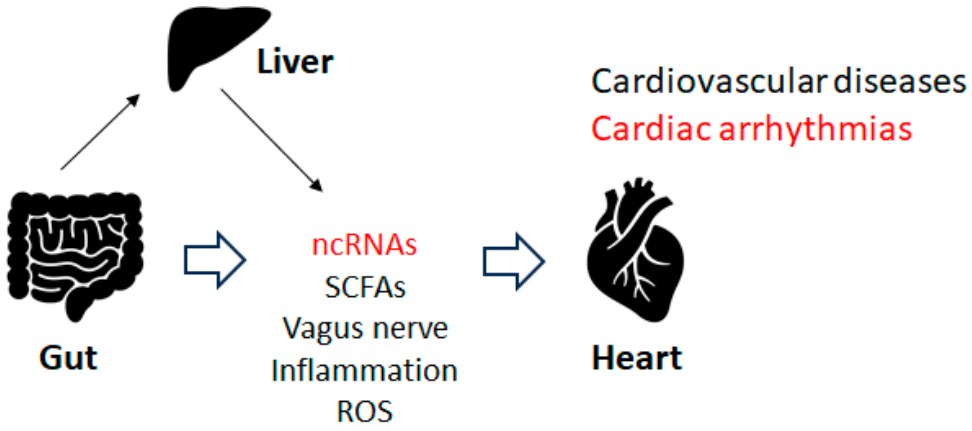

Figure 2. Several factors and/or inflammation with ROS may affect the development of cardiovascular diseases including cardiac arrhythmias. Note that some critical pathways have been omitted for clarity.

In these ways, evidence from numerous studies in both humans and animals suggests that the role of the gut microbiota and its metabolites in arrhythmia has been well established. Through a variety of pathways, the gut microbiota significantly affects cardiac arrhythmia, which may provide a wide range of potential therapeutic approaches [58, 59]. Linking the possible interfering role of gut microbiota in the pharmacokinetics of drugs used in management of cardiac arrhythmias would help to better understand the potential of probiotics [60, 61].

6. Immune pathway and cardiac arrhythmias

There is increasing attention on the molecular mechanisms controlling the onset and the progression points of cardiac arrhythmias to the complex cell to cell interplay that triggers immune cells enhancing atrial fibrosis [62]. The dysregulation of immune pathway might meaningfully contribute to ion channel dysfunction and the initiation of cardiac arrhythmias [63]. In turn, the interaction between immune cells and atrial myocytes may enhance atrial electrical and functional remodeling, which is responsible for the progression of cardiac arrhythmias [64]. Interestingly, some ncRNAs are involved in the ribonucleolytic cleavage with the target of mRNA [65], in which several members of the APRO family have been shown to be associated with the cytoplasmic mRNA deadenylation [66, 67]. Likewise, some of the APRO family proteins could interact with the poly (A) ribonuclease complex [68, 69]. These APRO family proteins (Btg1, Btg2, Tob1 and Tob2) might be a key modulator of microRNAs [70], which might be deeply involved in the regulation of immune cells [71]. Therefore, APRO family proteins have been shown to be involved in immune-related disorders including ulcerative colitis and cancers [72-74]. Interestingly, it has been shown that one of the APRO family member, BTG1, may be involved in the regulation of ion channel related gene expression [75, 76]. Remarkably, it has been shown that the BTG1 could promote the deadenylation and/or degradation of mRNA to secure T cell quiescence [77], suggesting that BTG1 might be involved in a key mechanism underlying T cell quiescence. In addition, another APRO family member, Tob1, might be a key regulatory molecule in the process of endothelialization in the repair progress of atrial septal defects [78]. Tob1 might also play a fundamental role in keeping cells to a quiescent position, thereby obstructing cellular proliferation of normal and/or cancer cells [79]. TOB1 is inactivated in many human cancers. Therefore, TOB1 has been considered as a tumor-suppressor protein [80].

7. Future perspectives

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Nevertheless, the immune-regulating potential of GM mediated some anti-cancer therapeutic functions, specifically anti-CTLA-4 and anti-PD-L1 targeting drugs that showed better outcomes in patients with some species of Bacteroides and Bifidobacterium, respectively [81, 82]. These actions are hypothesized to be related to the action of GM on DCs which are essential to trigger proper T-cells response [83]. Additionally, short-chain fatty acids (SCFAs) produced in the gut may modulate anti-CTLA-4 and anti-PD-1 stimulated immune responses and their anti-tumor efficacy [84]. SCFAs are characterized by containing fewer than six carbons, such as acetate, propionate, and butyrate, which are mainly produced by the gut microbiota as fermentation products. The human gut microbiota and/or their metabolites including SCFAs have also become a potential therapeutic target for the development of interventions for the prevention of cardio-metabolic disorders [85]. There are noteworthy associations between gut microbiota and the microglia in the brain, suggesting that the crosstalk of gut microbiota and nerve function, based on the roles of microglia [86]. Therefore, some modifications in the composition of gut microbiota might play a critical role in the pathogenesis of several diseases. Remarkably, we presume that cardiovascular diseases including cardiac arrhythmia might also relate to the pathogenesis that is based on the engram memory system [87-89]. **(Figure 3)** The engram memory system in the brain could retain the information of a certain inflammation in the body which might be involved in the pathogenesis of various diseases including cardiovascular diseases, in which the immunity-linked processes might be associated with the neuronal responses to memory engrams [90]. Future work should define at the molecular level how this pathway could precisely interfere to regulate the cardiac arrhythmias. In particular, forthcoming research should focus on the identification of disease-specific engram retention over time during the latent period of cardiovascular diseases.

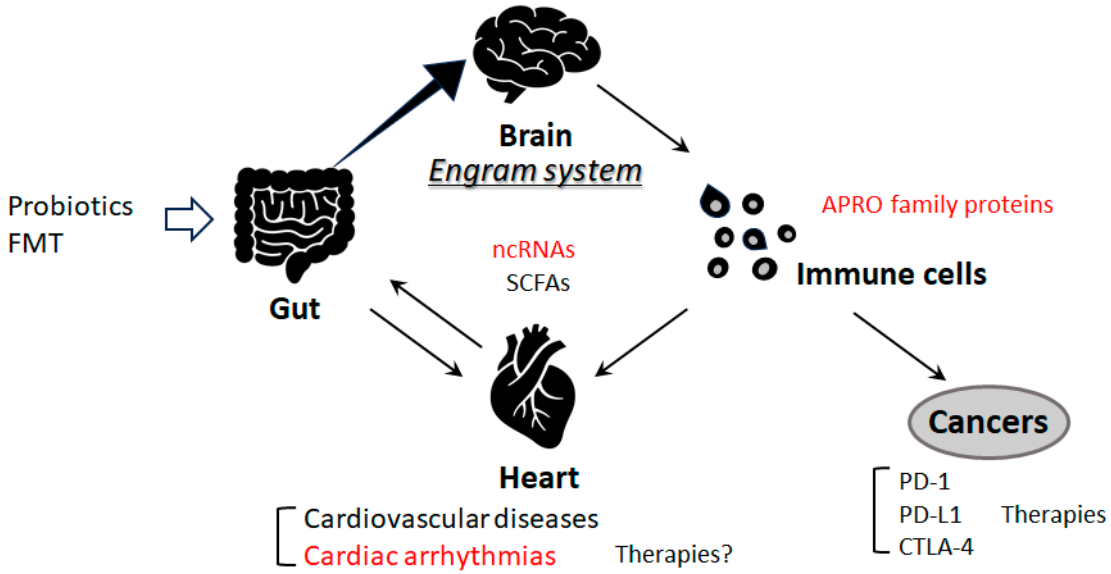

Figure 3. Schematic representation of the potential inhibitory tactics against the pathogenesis of cardiovascular diseases including cardiac arrhythmias. Some kinds of probiotics and/or fecal microbiota transplantation (FMT) could contribute to the alteration of gut microbial community for the alteration of ncRNA and/or SCFAs production, which could be beneficial for the treatment of cardiovascular diseases. Note that several important activities such as inflammatory reaction, autophagy initiation, and ROS production have been omitted for clarity.

8. Conclusion

Several ncRNAs could be involved in the development of certain cardiac arrhythmias, in which the association between gut and heart might play an important role. In addition, the correlation between gut and brain as well as the correlation between brain and immunity might also influence the development of cardiovascular diseases including cardiac arrhythmias. An in-depth knowledge

of the role of ncRNAs in cardiac arrhythmias may be valuable for progressing new clinical diagnosis and treatment.

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Abbreviations

APROs	anti-proliferative proteins
BTG1	B cell translocation gene 1
CNS	central nervous system
circRNA	circular RNA
CTLA-4	cytotoxic T lymphocyte-associated protein-4
FMT	fecal microbiota transplantation
LOC10	*LOC100911717*
lncRNAs	long non-coding RNAs
mRNA	messenger RNA
ncRNA	non-coding RNA
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
QOL	quality of life
ROS	reactive oxygen species
SCFAs	short-chain fatty acids
siRNA	short interference RNA
TASK-1	tandem of P domains in a fragile inner repairing K+ channel-linked acid-sensitive K+ channel 1
Tob1	transducer of ErbB2 1
UTR	untranslated region

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