Review

Gut Microbiota and Non-coding RNAs Might Be Involved in the Pathogenesis of Alcohol Dependence

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Review

Gut Microbiota and Non-Coding RNAs Might Be Involved in the Pathogenesis of Alcohol Dependence

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Abstract: A great deal of studies have assessed the expression of noncoding RNAs (ncRNAs) as well as their relevant molecular functions and biological mechanisms in the individuals of alcohol dependence. Alcohol dependence is one of the most prevalent neuropsychological disorders worldwide, and its pathogenesis is intricate and inadequately understood. There is considerable evidence demonstrating substantial links between multiple genetic factors and the development of alcohol dependence. Critical roles of ncRNAs have been emphasized in the pathophysiology of mental diseases including alcohol dependence. In the comprehension of ncRNAs action and their mechanisms of modification, they have emerged as therapeutic targets for a variety of psychiatric illness including alcohol dependence. Worth mentioning, dysregulated expression of ncRNAs has been regularly detected in individuals of alcohol dependence. An in-depth knowledge of roles of ncRNAs and m6A modification may be valuable for the development of a novel treatment against alcohol dependence. In general, a deeper comprehension of functional roles ncRNAs may make significant contributions to the precise diagnosis and/or actual treatment of alcohol dependence. Here in this review, we mostly focused on the up-to-date knowledge regarding alterations and/or modifications in the expression of ncRNAs in alcohol dependence, and then, presented their prospects for future research and therapeutic application with a novel concept of engram-system.

Keywords: ncRNA; lncRNA; miRNA; autophagy; gut microbiota; gut-brain axis; alcohol dependence; alcohol use disorder

1. Introduction

Alcohol dependence, which may include alcohol abuse and/or alcohol use disorder, is a kind of prolonged recurring psychiatric disease described by being unable to stop drinking without suffering withdrawal symptoms and/or continuing alcohol use in spite of destructive consequences. The representative symptoms may include habitual alcohol use, loss of regulation over alcohol consumption, and alcohol removal symptoms [1,2]. Probably, genes might be responsible for around half of the risk of alcohol dependence [1]. The consequences are connected with extensive disability as well as substantial medical and/or economic burdens [3], which becomes one of the most general mental diseases globally [4]. Hereafter, the term alcohol dependence practically equates with alcohol addiction, alcohol abuse, alcoholism, and/or alcohol use disorder.

Chronic alcohol exposure yields general neuroadaptations or alterations in gene expression in alcohol dependence [5]. It has been assumed that the controlling system in which non-coding RNAs (ncRNAs) may partake in affecting potential molecular targets of certain signaling pathway that control biological and cellular outcomes, eventually leading to the incidence and/or progress of alcohol dependence. ncRNAs are various bioactive molecules that are generally existing in organisms, mediating multiple biological processes including mRNA splicing, regulation of translation, and/or post-transcriptional modification for altered intracellular signal transduction [6]. A number of investigations grounded on recent biotechnologies have shown that ncRNAs are typically plentiful in central nervous system (CNS) and play a key role in brain homeostasis as well

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as the pathological progressions of a psychiatric disease via epigenetic mechanisms [7]. ncRNAs have been shown to regulate a variety of ion channels and/or intercellular linking proteins/molecules. Thousands of unique ncRNAs sequences subsist inside cells, which organize a part of the transcriptional background [8]. ncRNAs are kinds of well-designed machineries for defined gene expression with heterogeneous subsets, which could be further separated into microRNAs (miRNAs), long non coding RNAs (lncRNAs), circular RNAs (circRNAs), piwi interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and so forth [9]. Understandings into the possible roles of these ncRNAs in the development of several diseases, predominantly in brain neurological diseases, have compelled ncRNAs potential tools for innovative therapeutic approaches. Dysregulation of these ncRNAs, particularly circRNAs, miRNAs, and lncRNAs has been detected in human individuals of alcohol dependence, which might be related with the beginning and/or advancement of the disorder [10]. (Figure 1)

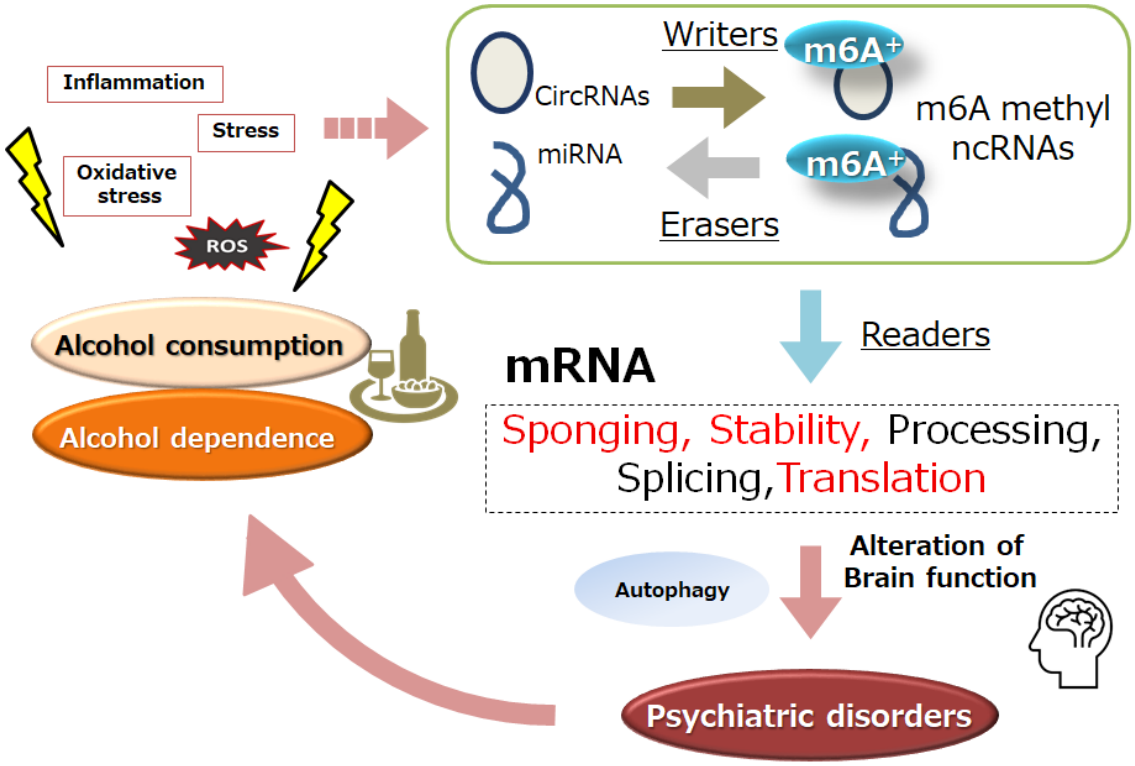

Figure 1. Representation for the association of non-coding RNAs (ncRNAs) and m6A modification (m6A$^+$) of ncRNAs to psychiatric disorders and/or alcohol dependence. Firstly, the m6A modification may be controlled by methyltransferases "writers" and demethylases "erasers" by the stimulation of inflammation and/or oxidative stress with reactive oxygen species (ROS). The ncRNAs and m6A-ncRNAs with binding "readers" molecules may contribute to several RNAs activities including sponging, stability, processing, and/or translation of mRNAs, which could be consequently an important process several psychiatric disorders including alcohol dependence.

Epigenetics is a field that investigates genetic alterations in gene expression that do not include changing the DNA sequence. Foremost epigenetic mechanisms contain the well-known regulation by above-mentioned ncRNAs, histone modifications, and DNA/RNA methylation, which are in an area of continuing investigation. In particular, a diverse of studies have suggested that ncRNAs may play an important role in epigenetic control [11]. In addition to genetic variation, various stressors including psychological stressors and environmental social factors can lead to alcohol dependence *via* epigenetic modifications at the transcriptional level of RNAs [12–15]. Here, we digest recent research progresses for the purpose of approaching to a superior understanding of ncRNAs/epigenetics and their mechanisms during the pathogenesis of alcohol dependence, which

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may contribute to gaining a comprehension on the underlying mechanisms for the superior development of tactics against alcohol dependence.

2. Alcohol Dependence and ncRNA

The profile of miRNAs expression has shown that some miRNAs are abnormally expressed in patients with alcohol dependence, which may be involved in the progression of alcohol dependence through several biological mechanisms. For example, more than 35 miRNAs including hsa-miR-553 and let-7f are considerably up-regulated in the individuals of alcohol dependence compared with healthy controls [16]. Plasma miRNAs profiling/analysis has also shown that the concentrations of miR-122-5p, miR-193b-3p, miR-3937 and miR-4507 in plasma are associated to the alcohol consumption, which may play a key role in the pathogenesis of alcohol dependence [17]. The miRNAs-dependent regulation of target genes might be also critical for the pathogenesis of alcohol dependence. Likewise, dysregulated lncRNAs may be found in the brain of individuals with alcohol dependence being related to their pathophysiology, one of which may contribute to the abnormal expression of brain-derived neurotrophic growth factor (BDNF) in patients with alcohol dependence [18]. The expression of several lncRNAs including SNORD3C, HSPA7, and RP11-543H23.2 has been aberrantly detected in different brain regions of patients with alcohol dependence. Some lncRNAs including NCRNA-00051 or 00176 and 00107 are also expressed higher in the prefrontal cortex of individuals of alcohol dependence compared with healthy controls. These lncRNAs may be related to the dysfunction of splicing factors by regulating some post-transcriptional processes [19]. There are more than a few lncRNAs, which are significantly decreased in individuals with alcohol dependence [20].

Furthermore, an accumulating body of research has also emphasized the stimulating views of circRNAs as diagnostic markers for alcohol dependence. Expression of serum hsa-circ-0002130 or 0004771 in patients with alcohol dependence are considerably higher than those of healthy control individuals. Therefore, the hsa-circ-0004771 could be a susceptible diagnostic biomarker. Mechanistically, differentially expressed circRNAs may interact with several alcohol dependence - related miRNAs, which could affect inflammatory pathways [21]. Interestingly, decreased expression of circRNA-406742 can be found in patients with alcohol dependence, which is negatively correlated with miR-1200 expression [21]. Besides, the circRNA-000480 and/or 104942 are highly enriched in patients with alcohol dependence and/or psychiatric disorders [22]. CircRNAs may function as a sponge of miRNAs to affect neural function through the regulation of target genes.

In these ways, a substantial body of research conducted by evolving biotechnologies has highlighted the crucial roles of several ncRNAs in the pathophysiology of mental diseases and alcohol dependence [7,23]. About 10 % of miRNAs are downregulated in alcoholism, including miR-126, miR-153, miR-432, and miR-567 [23]. Unlike the relatively stable genetic code, this combinatorial ncRNAs epigenetic code may be vigorously reprogrammed as a cause or consequence of psychiatric disorders and/or alcohol dependence [24]. From normal development and physiology to the regulation of diseases including alcoholism and/or several psychiatric disorders, some ncRNA molecules have been discovered to mediate diverse processes in CNS [5,25]. For example, ncRNAs may be developed as therapeutic agents to protect the blood-brain barrier for CNS damage patients [25].

3. Alcohol Dependence and m6A Modification of RNAs

Alterations of epitranscriptome could authenticate their investigation as an imperative modulator. In general, the epitranscriptome encompasses all post-transcriptional modifications that occur on RNAs. The most prevalent modification is methylation of N6 adenosine (m6A) that occurs on specific sequence contexts of RNAs [26], which can change the function and/or regulation of their RNA targets. Environmental factors including anxiety, stress and/or social pressure as bad as chronic alcohol usage could lead to alcohol dependence through epigenetic regulation and/or remodeling of chromatin. Environmental effects could also lead to epigenetic modifications at post-transcriptional levels. The m6A is the most well known modification of eukaryotic RNAs, which could regulate

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transcript splicing, stability, translation, and ncRNA binding. [27]. Chronic ethanol exposure may alter levels of some ncRNAs methylation as well as certain mRNA methylation and their expression levels, suggesting a potential mechanism of epitranscriptome by which chronic alcohol usage could remodel the expression of alcohol responsive genes in the brain, therefore enhancing the risk of development of alcohol dependence [28]. Strikingly, in human postmortem amygdala of early onset alcohol dependence, *brain-derived neurotrophic factor (BDNF)-antisense* lncRNA is hypomethylated leading to decreased expression levels of BNDF [29]. In the context of alcohol intoxication, the up-regulation of the lncRNA could ameliorate BDNF expression, in which BDNF-AS seems to be regulated by diminished levels of m6A [29]. BDNF belongs to the neurotrophin family with familiar roles in neural development and/or synaptic plasticity. Therefore, lncRNAs may play imperial roles in the control of BDNF expression [30].

The m6A is a pervasive mRNA modification in eukaryotic cells, which arises from the action of methyltransferases, methylation-binding proteins, and demethylases. m6A methylation of RNAs is related with various neurological disorders including depression, epilepsy, Parkinson's disease, Alzheimer's disease, brain injury, and brain gliomas. Therefore, m6A-related drugs have appealed great concerns in the therapeutic fields of neurological disorders [31]. A number of the signaling pathways in brain have been realized to be mediated through m6A modification, but only a few investigations have directly explored the effects of m6A on depression and/or depressive-like behaviors. Depression is a frequent psychiatric disorder described by continued low mood which may be associated with m6A methylation. Therefore, the m6A related molecules including METTL3, METTL14, ALKBH5 and WTAP are associated with major depression [32]. In addition, the gene expression level of m6A controllers in depressive-like behaviors [33]. Interestingly, it has been reported that regulation of m6A is compromised in patients of major depressive disorder following glucocorticoid receptor stimulation [34].

Related proteins of m6A modification could play key roles in the progress of several neuropsychiatric disorders including depression, Parkinson’s disease, and Alzheimer’s disease. The m6A modification regulation mechanism in CNS during the development of neuropsychiatric disorders may provide some insight into new research targets and treatment directions [35]. Similarly, the disturbance of m6A modification may be one of the most important causes for the atypical function of CNS leading to the occurrence of CNS diseases including depression [36]. Serious drinking may lead to neuronal atrophy associated with increased risk for anxiety, depression, cognitive deficits, and altered regulation over drinking behaviors [37]. In addition, chronic stress, anxiety, and depression may be key risk factors for developing alcohol dependence [38]. In fact, depression is often comorbid with alcohol dependence with severe stress components [39]. (Figure 1)

4. Individual Epigenetic Mechanisms for Alcohol Dependency

There is a huge body of evidence exhibiting that alcohol could alter gene expression through epigenetic processes [40]. Epigenetic mechanisms, such as acetylation of the N-terminal tails of histones that pack up DNAs to nucleosomal remodeling, could cause transcriptional change in addiction, which may recompense related genes in specific bain regions contributing to the helpful phenotype such as alcohol tolerance. Studies that exploit alcohol withdrawal to bring depressive-like behaviors have assumed different ways and intervals of alcohol exposure and withdrawal. However, a relationship might exist between individual sensitivity to the aversive properties of ethanol and risk for alcohol dependency. An important confusing factor to deliberate is that the molecular changes induced by alcohol consumption itself and withdrawal from habitual alcohol use may not be related to the depressive-like behavior. Therefore, it might be important to establish a causal role for specific epigenetic mechanisms and alterations of gene expression induced by alcohol explicitly in depressive-like condition [41]. Epigenetic mechanisms may also play an imperative role in depression [42]. Analytical methods of genome-wide DNA methylation and histones modification profile have delivered respected information to establish the functional role of histone-modification could indicate on specific genes [43]. Alcohol dependency may actively lead to relaxed chromatin

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because of the downregulation of DNA/histone methylation. Otherwise, chronic exposure might in part lead to close-fitting chromatin bundle. Consequently, alcohol drinking may affect epigenetic mechanisms responsible for adaptation alterations of several brain paths probably linked to stress management [44]. After withdrawal, chromatin may tend to the condensed state via the upregulation of DNA and/or histones [45]. For example, mRNA expression levels are significantly lower compared to controls, which correspond to alterations in DNA methylation in a rodent model [46]. Therefore, DNA methylation might be a target for pharmacological interventions for alcohol dependency [46]. In addition, DNA methylation could be a good biomarker of alcohol consumption [47]. Exposure to ethanol during adolescence might upregulate DNA methyltransferase activity, which can induce hypermethylation of various genes such as coding for neuropeptide Y (NPY) and BDNF [48]. Furthermore, prenatal exposure to alcohol may generally trigger epigenetic modifications depending on the development stage, which may contain increased histone acetylation and/or reduced DNA/histone methylation [49]. In this regards, alcohol withdrawal may lead to dysregulated histone acetylation via the increased expression of histone deacetylase (HDAC) in some brain areas [50]. Hence, the treatment with HDAC inhibitors can amend negative emotional conditions brought by alcohol withdrawal [50]. However, histone acetylation in the brain of depression-like behavior through withdrawal after alcohol exposure may require further intensive examination.

5. A Relationship between Gut Microbiota and Alcohol Dependency

Gut microbiota have various effects on host physiology, including host metabolism, the development of immune system, and even behaviors [51]. The intricate interaction among the gut, stress, and eating/drinking behavior may simplify new therapeutic targets for stress-related psychiatric disorders [51]. Remarkably, short-chain fatty acids (SCFAs), explicitly acetate, propionate, and butyrate, might be interaction-mediators of microbiota-gut-brain axis on the stress response and/or eating/drinking behavior. In fact, various metabolites from the gut microbiome including SCFAs have been proved to regulate the histone acetylation process [52]. The microbiota-gut-brain axis may be a bidirectional route of homeostatic communication via epigenetic mechanisms of diverse metabolites such as SCFAs. Thus, a modulation of gut microbiota via diet or lifestyle can regulate neuron/brain inflammation via certain epigenetic mechanisms [53], which might be effective for emotional status and/or depressive disorders [54]. As important constituents of epigenetics by gut microbial metabolites and/or fermentation products, several miRNAs with epigenetic mechanisms have vital roles in various physiological homeostasis mechanisms [55,56]. For example, microbial acetate and/or butyrate might alleviate obesity with the regulation of host miRNAs [57]. In addition, there were close intricate interactions among gut microbiota, inflammation and differential miRNAs suggesting that ncRNA may possess a potential role in the protection of host against life-related diseases such as atherosclerosis [58]. Interestingly, it has been shown that circRNAs and the gut microbiome can interact to influence the growth of cancer cells [59]. Similarly, expression of lncRNAs could be repressed by gut microbiota [60]. Increasing data suggest that regulatory ncRNAs including miRNAs, circRNAs, and lncRNAs may influence host-microbe interactions showing as potential biomarkers in microbiome-associated disorders including diabetes and cancers [61]. (Figure 2)

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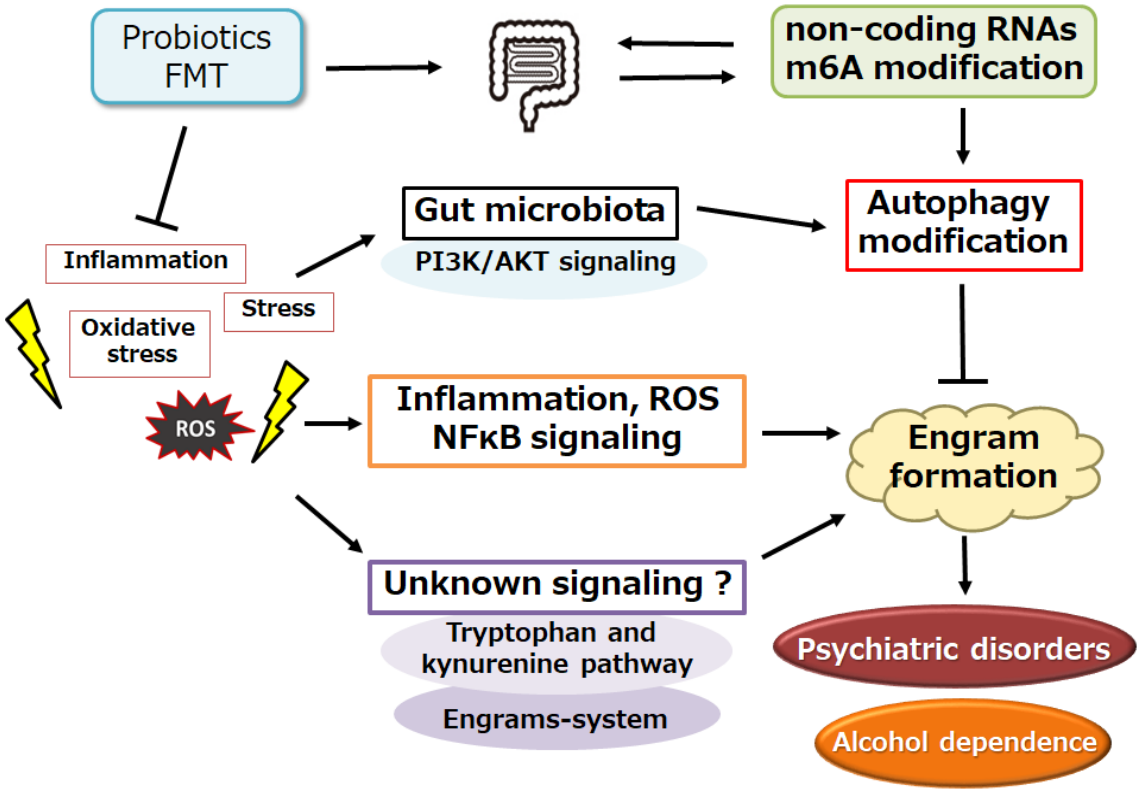

Figure 2. Schematic demonstration of the potential strategies against the pathology of alcohol dependence. Various kinds of probiotics and/or fecal microbiota transplantation (FMT) may support the alteration of gut microbiota for the modification of autophagy, which might be advantageous for the inhibition of several engram formation, which may consequently improve the pathology of psychiatric disorders including alcohol dependence. Note that some of significant events such as autophagy initiation, ROS production, and inflammatory reactions have been misplaced for clarity.

In addition, the gut microbiota has an effect on host m6A mRNA modifications, which is another demonstration of the interaction between gut commensal bacteria and their hosts [62]. As well, the host m6A modification can also influence the gut microbiome by provoking gut inflammatory responses [63]. Possibly, *Lactobacillus plantarum* and/or *Akkermansia muciniphila* can influence the specific m6A modifications, which might emphasize epitranscriptomic modifications as a communication between gut commensal bacteria and host [62,64]. The presence of certain gut microbiome may also account for the considerably elevated m6A levels in the intestine [65]. Thus, m6A methylation is indeed implicated in the host-gut microbiota crosstalk. Actually, substantial studies have suggested that the enteric microbiome is a key mediator of m6A modification. In general, a number of ncRNAs and/or m6A modification have been associated in the beginning and progression of drug addiction [66,67]. Therefore, the gut-brain axis may be the key to the homeostasis of CNS, which may regulate several neuro-behaviors [68]. The gut microbiome could also affect drug bioavailability, blood-brain barrier (BBB) permeability, and social behaviors [69]. Emerging microbiota-based interventions such as prebiotics, probiotics, FMT, or metabolites supplementation might advocate an exciting tactic to treating psychiatric disorders probably including alcohol dependency.

6. A Possible Tactic with Alteration of Gut Microbiota against Alcohol Dependency

Too much alcohol consumption may induce gut dysbiosis, an imbalance in gut microbiota, through numerous mechanisms. Consequently, chronic alcohol exposure can reduce the creation of mucus and several peptides, which may intrude the intestinal barrier [70]. Although pharmacological treatments are existent, their effectiveness depends on appropriate faithfulness to the prescribed

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regimen [71]. Therefore, most patients with alcohol dependency are left untreated, and there is a need for additional, more effective therapies. Identifying some biological markers predicting susceptibility to develop extreme alcohol consumption may lead to an enhancement of good clinical care. Interestingly, relationships between gut microbiota and behavioral characters that individualize alcohol dependency has been described [72]. Certain microbiota composition is linked to addiction actions in a realistic model of alcohol dependency [72]. Based on this findings, newfangled therapeutic regimens should embrace gut microbiome manipulation, which may lessen alcohol intake and/or drinking activities. Indeed, alcohol consumption produces both direct and/or indirect consequences on the gut microbiota through metabolism, neuronal response, and immune inflammatory cascades. In particular, chronic inflammatory condition may lead to alterations in several inflammatory mediators that can activate nuclear factor kappa B (NF-kB) signaling pathway leading to neuronal damage/apoptosis in glial and/or neuronal cells [73]. It is imperative to note that not all patients with alcohol dependency have dysbiosis and/or increased gut epithelial disrupton [74]. However, several effects of alcohol on the gut microbiome might contribute to the increased alcohol consumption. Therefore, use of probiotics, prebiotics, or FMT may deserve further investigation as therapeutic tactics for alcohol dependency [74]. At present, however, the application of FMT as a beneficial therapeutic approach is yet in the investigatory stages [74]. In addition, donor-to-recipient disease of stool transfer may be a great fear of the FMT. Moreover, it still requires to be determined what bad effect of FMT has on the gut microbiota and/or to the brain in the long run. [75]. (Figure 2)

Interestingly, an antidepressant arketamine (also termed R-ketamine) can renovate the altered composition of gut microbiota within patients of depression-like behaviors in rodents, contributing to valuable effects of the R-ketamine. Ketamine is a racemic mix composed of two enantiomers, R-ketamine and esketamine (S-ketamine). Importantly, both enantiomers have shown antidepressant effects, whose effects are attributed to distinct pharmacological activities including NMDA-channel and/or opioid receptor. It has been shown that antidepressant-like effects of both ketamines might be in part mediated by alteration of gut microbiota [76]. Ketamine could potentially activate several biochemical signaling pathways which may eventually lead to inhibitory phosphorylation of GSK3β molecule in microglia [77]. Remarkably, S-ketamine exerts the neuroprotective effects via enhancing autophagy lessening oxidative stress, whose mechanism comprises AMPK/mTOR-dependent autophagy and/or antioxidant system [78]. Amazingly, the S-ketamine considerably could change the abundance of gut microbiota including *Adlercreutzia equolifaciens* and *Akkermansia muciniphila* [79]. It has been revealed that the regulation of NFAT signaling by miR-149 might play a key role in tenacious prophylactic effects of R-ketamine in inflammation, and that gut microbiota can control the gene expression of miRNAs via the gut-brain axis [80]. Increased miR-149 expression may be related to the reduced glial cell numbers in patients diagnosed with familial bipolar disorder [81]. Because miR-149 has been revealed to inhibit glial proliferation, increased miR-149 expression is also consistent with the pathology of depressive disorder [82]. Still, there is rarely information presenting the role of other miRNAs or m6A modification in the prophylactic effects of ketamine and its enantiomers in brain neuroinflammation disorders.

7. Future Perspectives

Would you like to use ketamine for improving alcohol dependency? Come to think of it, there might be a dangerous choice. In other words, it would be difficult to answer, which is better and/or safer either ketamine abuse or alcohol abuse. Based on a hypothesis if the ketamine may improve alcohol dependency via the mechanism of improving autophagy in neuronal cells, dietary intervention would be possible for the treatment of alcohol dependency. Because, the modification of gut microbiome is safely imaginable via a diet, which could also contribute to the alteration of ncRNAs production and/or m6A modification in various cells [83,84]. In fact, some dietary supplements are dynamically performing through different mechanisms to reduce alcohol relapse [85]. As for prebiotics and/or probiotics, those interventions may be somewhat inadequate for a treatment in regard to the improvement by autophagy [86,87]. Some additional factors and/or

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signaling activation might be required for the superior dietary intervention even against alcohol dependency. In addition to modulating the gut microbiome, for example, metformin could exert its positive effect by affecting mitochondrial function and restoring of redox balance [88]. In addition, several elements involved in the tryptophan and kynurenine pathway may also be plausible, which has been presented to be linked to various immune-related diseases including major depressive and bipolar disorders [89]. Formed by recurring inflammatory conditions, an "engram" might devote to a gentle development of these diseases [89]. Engram memory system in brain might retain the knowledge of a certain inflammation in a body which would be involved in the pathogenesis of immune-related diseases, in which the immunity-linked routes might be also related with the neuronal responses to memory engrams [90]. Clearance of the bad memory "engrams" could be promising for the prevention and/or treatment against an immune-related disease even as well a cancer, a cardiac arrhythmia, and/or a neurodegenerative disease [83,91,92]. (Figure 3) If that is the case of alcohol dependence, a certain adjustment of "engram" with the alteration of gut microbiota might be helpful for a notable treatment tactic against alcohol dependence. Future work should precisely explain at the molecular level how this engram pathway could interfere to progress the alcohol dependency. (Figure 3)

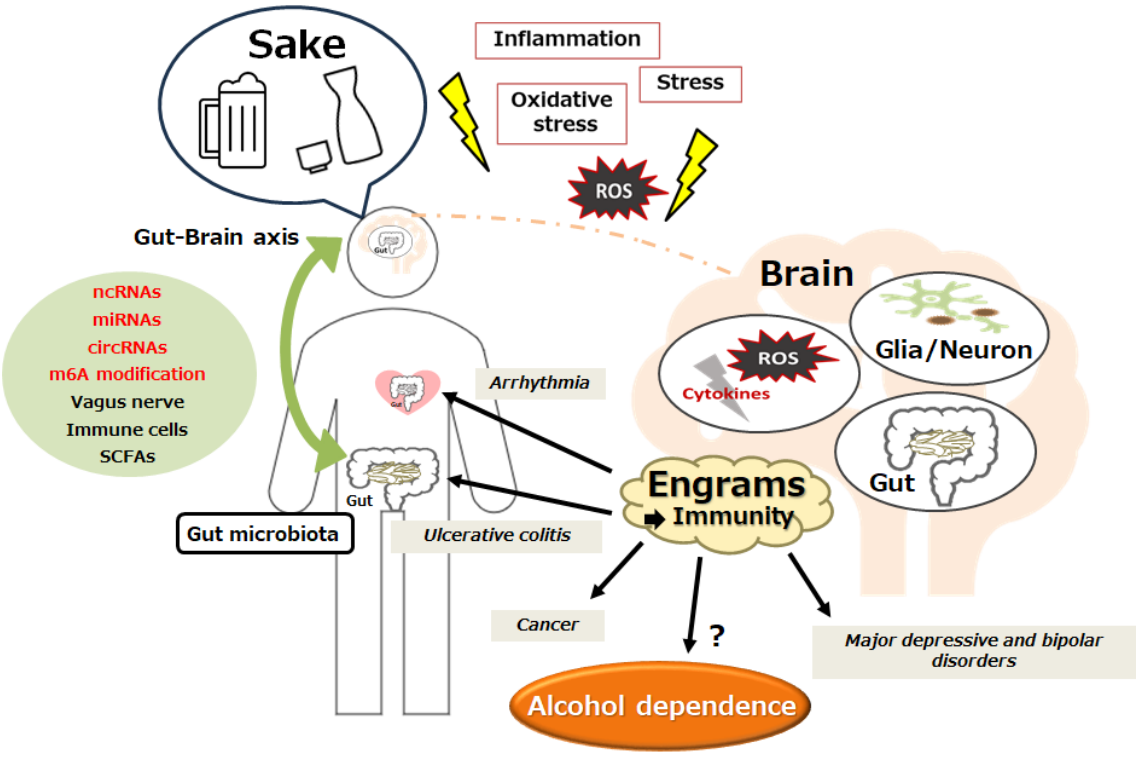

Figure 3. Schematic impression for the pathogenesis of immune-related diseases such as cardiovascular diseases, acute kidney injury, chronic kidney disease, inflammatory bowel disease, major depressive disorder, bipolar disorder, and alcohol dependence. The gut–brain axis with the utilization of ncRNAs, m6A modification, and/or short chain fatty acids (SCFAs) may contribute to the pathogenesis of immune-related diseases through the formation of several "Engrams" in brain. Inflammation with reactive oxygen species (ROS) may be also involved in the pathway for the modification of immune cells. Note that several important events such as cytokine induction or anti-inflammatory reactions have been omitted for clarity. "?" means for author speculation.

8. Conclusion

Several ncRNAs and/or m6A modification might be involved in the instigation of alcohol dependency, in which the relationship between gut and brain can play an important role. Also, the correlation between brain and immunity might also influence the development of alcohol

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dependency. An in-depth knowledge of roles of ncRNAs and m6A in gut microbiome may be valuable for the development of a novel treatment against alcohol dependence.

Abbreviations

BBB	blood-brain barrier
BDNF	brain-derived neurotrophic growth factor
CNS	central nervous system
circRNA	circular RNA
FMT	fecal microbiota transplantation
HDAC	histone deacetylase
lncRNAs	long non-coding RNAs
mRNA	messenger RNA
m6A	methylation of N6 adenosine
ncRNA	non-coding RNA
NF-kB	nuclear factor kappa B
NPY	neuropeptide Y
piRNAs	piwi interacting RNAs
siRNAs	small interfering RNAs
ROS	reactive oxygen species
SCFAs	short-chain fatty acids
siRNA	short interference RNA
R-ketamine	arketamine
S-ketamine	esketamine

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