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Review Article

Comprehension of gut microbiota and microRNAs may contribute to the development of innovative treatment tactics against metabolic disorders and psychiatric disorders

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Abstract: Metabolic syndrome is a group of pathological disorders increasing the risk of serious diseases including cardiovascular disease, stroke, type 2 diabetes. Global widespread of the metabolic syndrome has put a heavy social burden. Interestingly, a crucial link between the metabolic syndrome and a psychiatric disorder may frequently coexist, in which certain shared mechanisms might play a role for the pathogenesis. In fact, some microRNAs (miRNAs) have been detected in the overlap pathology, suggesting a common molecular mechanism for the development of both disorders. Subsequent studies have revealed that these miRNAs and several metabolites of gut microbiota such as short chain fatty acids (SCFAs) might be involved in the development of both disorders, in which the association between gut and brain might play key roles with engram memory for the modulation of immune cells. Additionally, the correlation between brain and immunity might also influence the development of several diseases/disorders including metabolic syndrome. Brain could possess several inflammatory responses as an information of pathological images termed engrams. In other words, preservation of the engram memory might be achieved by a meta-plasticity mechanism that shapes the alteration of neuron linkages for the development of immune-related diseases. Therefore, it might be rational that metabolic syndrome and psychiatric disorders may belong to a group of immune-related diseases. Disrupting in gut microbiota may threaten the body homeostasis, leading to initiate a cascade of health problems. This concept may contribute to the development of superior therapeutic application with the usage of some functional components in food against metabolic and psychiatric disorders. This paper reviews advances in understanding the regulatory mechanisms of miRNAs with the impact to gut, liver and brain, deliberating the probable therapeutic techniques against these disorders.

Keywords: Metabolic syndrome, psychiatric disorder, ncRNA, miRNA, gut microbiota, engram, immune related disease

Introduction

Conditions of metabolic syndrome may contain central obesity with high blood pressure, hyperglycemia, and insulin resistance [1], which is a group of pathological settings that occur together, increasing the risk of several more severe disorders/diseases including stroke, cardiovascular disease, type 2 diabetes mellitus (T2DM), and so on. The insulin resistance seldom happens on its own, which may set up a clinical part of metabolic syndrome along with central obesity [1]. The T2DM and metabolic syndrome indicate tightly interlinked public health challenges [2]. Therefore, identifying particular factors connected to the development of metabolic syndrome may be of great health interest. In particular, the T2DM is the most common chronic metabolic disorder affecting adults, which has exhibited much research interest worldwide. When coexisting with the T2DM, metabolic syndrome could aggravate the progression of the disease and significantly enlarge the risk of cardiovascular diseases [3], which are the prominent cause of mortality [4]. Metabolic syndrome may result from an intricate interaction between heredity along with other risk factors such as physical

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inactivity, smoking, an unhealthy diet, and excessive alcohol consumption [5].

Major depressive disorder, one of the most widespread mental disorders, may include symptoms such as depressed mood, decreased interest, weight loss, insomnia, and repeated feelings of suicide [6]. Interestingly, depression may be associated with an increased risk for diabetes and cardiovascular disease as a comorbidity in patients [7]. It has been shown that the major depressive disorder has a frequent complication of diabetes, in which long non-coding RNA (lncRNA) may play an imperative role in the pathological progression [8]. In addition, the T2DM could exacerbate the major depressive disorder, while the major depressive disorder is connected with higher mortality within the patients of T2DM [9]. It has also been described that the relationship between T2DM and mood disturbance disorder may be mostly mediated by insulin resistance [10]. Therefore, treatment of the major depressive disorder with drugs for the T2DM could significantly improve the depressive condition, which suggests a shared mechanism for their molecular pathogenesis [11]. Although the bidirectional linkage between the T2DM and several psychiatric disorders has been recognized, the detailed molecular mechanisms underlying the relationship have remained unclear [12].

Psychological stress, lifestyle stress, and/or oxidative stress are well known to increase the risk of mental disorders such as major depressive disorder, bipolar disorder, schizophrenia, alcohol use disorder and/or metabolic disorders such as metabolic syndrome [13]. These various stresses characterized by different extrinsic or intrinsic stimuli are also a frequent threat for the homeostasis of individuals. Brain could respond to these stresses by triggering the adaptive system to start compensatory responses for sustaining homeostasis. However, obesity, inflammation, and/or excess oxidative stress may lead to the development both of metabolic disorder-associated fatty liver disease (MAFLD) and mental disorders [14], which have been considered to be key factors for the pathogenesis of these diseases/disorders [15]. In fact, depression and liver disease seem to be closely associated. Some patient with hepatitis and/or liver cirrhosis might exhibit depressive symptoms. On the other hand, some patients with the major depressive disorder may often develop an alcohol use disorder. A crucial linkage between psychiatric disorders and metabolic disorders seems to exist, in which certain shared molecular mechanisms may play a pivotal role. In the mechanism, gut microbiota might play an important role for the pathogenesis. Because, it is well-known that the gut-liver and/or the gut-brain axis may be imperative for the regulation of stresses. It looks no relationship between metabolic disorders and mental diseases, however, there might be substantial connection via the role of the gut-liver-brain axis. Here, this review may report recent works describing the molecular pathogenesis related to psychiatric and metabolic disorders for the development of superior therapeutic application against these disorders.

Several miRNAs found to overlap pathology between metabolic syndrome and psychiatric disorders

Small non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), have appeared as promising candidates for important biomarkers of several disorders and/or diseases. Because, they can play a vital role in replication, transcription, translation, and epigenetic regulation. In addition, they could also participate in several cellular key processes such as proliferation, differentiation, apoptosis and/or metabolism. Especially, several ncRNAs have been pushed as potential diagnostic and prognostic biomarkers for various diseases. For example, the diagnostic value of miR-182-5p has been evaluated for prediabetes and T2DM [16]. In addition, topical studies have indicated correlations between circular RNAs (circRNAs) and psychiatric disorders. Markedly, overexpression of circPTK2 may be associated with depressive-like behaviors [17]. Further mechanism research has revealed that circPTK2 may work as the sponge for miR-182-5p, which can contribute to the advantageous effect of circPTK2 [17].

As for a widely-known neuropsychiatric disorder, the exact pathogenesis of major depressive disorder remains obscure. However, miR-206 has been shown to regulate the biosynthesis of brain-derived neurotrophic factor (BDNF), a standard target involved in antide-

pressant and/or depression responses, suggesting that the miR-206 and BDNF may play an important role in the development of depression [18]. Incidentally, the miR-206 is usually known as having two forms of miR-206-3p and miR-206-5p. Interestingly, glucose-lowering drugs ordinarily treating for T2DM may influence the expression of circulating miR-206 within serum of patients with T2DM [19]. Bipolar disorder is a common, recurrent psychiatric disease with unidentified pathogenesis. Current studies have suggested that miRNAs levels of miR-149 and miR-29c in brains of patients with bipolar disorder are meaningfully changed, which may suggest an insight into the pathology and/or pathogenesis of bipolar disorder [20]. Interestingly, the miR-149-5p has been identified in several metabolic diseases including diabetes [21]. In addition, overexpression of miR-149-5p can protect against impairment of insulin secretion and cell apoptosis induced from high glucose condition, which may reduce the production of reactive oxygen species (ROS) [22]. There might also be alterations in the expression of miRNAs including miR-29c, miR-145, and miR-143 [23]. These miRNAs might be involved in intracellular glucose homeostasis, glucose neogenesis, glucose reuptake and/or insulin signaling [23]. Evolving evidence has also revealed that miRNAs can play a vital role in the pathogenesis of several alcohol use disorders. For example, elevated expressions of miR-34a and/or miR-34c may be detected in the group with alcohol use disorder in comparison with the control healthy group without alcohol use disorder [24]. The functional role of the miR-34a may also be involved in the pathophysiology of T2DM [25]. In addition, chronic ethanol consumption may be associated with diabetes, presenting the expressional alteration of miR-155 and miR-199 [26].

In short, these miRNAs detected in overlap pathology between metabolic syndrome and psychiatric disorders may suggest a common molecular mechanism for the both pathogenesis (**Figure 1**). In line with this, convincing evidence from epidemiological investigations implies that some components of metabolic syndrome may share the underlying common mechanism for the pathogenesis [27, 28]. Therefore, the relationship between metabolic syndrome and common mental health disorders should be furthermore highlighted [29, 30].

miRNA, SCFAs, and autophagy involved in the regulation of major depressive disorder and metabolic syndrome

In addition to the involvement of miRNAs, short chain fatty acids (SCFAs) may also be involved in the pathogenesis of major depressive disorder and metabolic syndrome. The SCFAs, including acetic acid, propionic acid, and butyric acid, are important metabolites of gut microbes that are generated predominantly by the gut fermentation of dietary fiber [31]. These metabolites can modulate the pathology of a number of diseases by inducing epigenetic alteration through DNA methylation, histone modification, and ncRNAs-associated gene silencing. SCFAs, especially butyrate, are well-known histone deacetylases inhibitors. Increasing studies have emphasized the significant role of SCFAs as emerging therapeutic targets for metabolic disorders such as T2DM [32]. In addition, it has been shown that levels of SCFAs radically increase when the severity of T2DM may be decreased by an intervention [33]. In addition, SCFAs have been recognized to exert advantageous effects on obesity and cardiovascular diseases [34, 35]. Levels of SCFAs and their biosynthesis in metabolic patients who respond to physical exercise are also heightened, implying the involvement of SCFAs during physical exercise mediated improvement on the metabolic disorder [36]. Some evidence have suggested that SCFAs can modulate the process of pathology via enhancing autophagy, which suggests that this protection may be associated with low levels of local and/or systemic inflammation, several cellular oxidative stress, and cellular apoptosis [37]. The reduction of apoptosis levels could be explained due to the reduction of inflammation or the activation of autophagy signaling pathway. Additionally, it has been shown that butyrate could induce autophagy as a protection tactic to impede mitochondrial apoptosis induced cell death [38]. Acetate could also induce autophagy and thereby hinder the apoptosis [37, 38].

SCFAs are natural ligands for free fatty acid receptors 2 and 3 (FFAR2/3), which are broadly found in endocrine and/or neural cells [39].

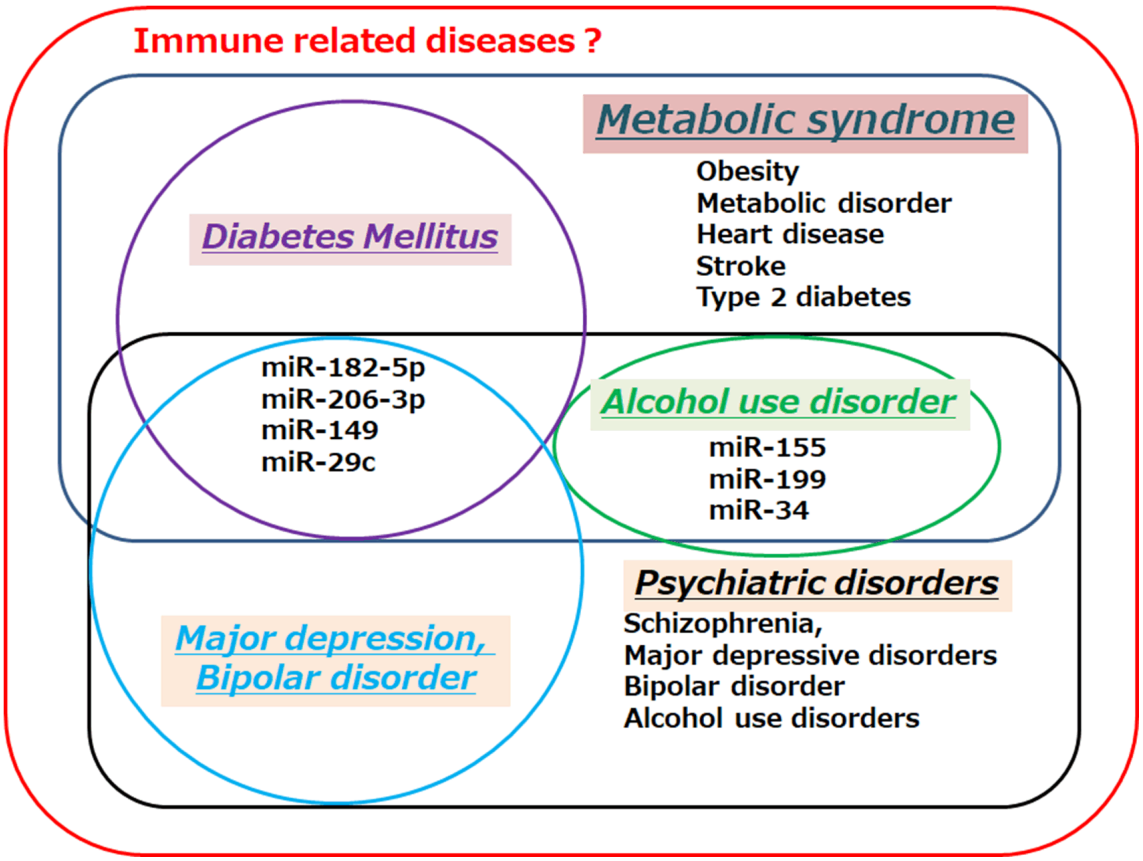

Figure 1. Schematic representation of several ncRNAs found in overlap pathology between metabolic syndrome and psychiatric disorders. In particular, the miR-182-5p, miR-206-3p, miR-149, miR-29c may be detected to overlap between type 2 diabetes mellitus and major depression disorder, whereas the miR-155, miR-199, miR-34 may be detected in patients of alcohol use disorder that is also believed as an overlap pathology between metabolic syndrome and psychiatric disorders.

Several studies have suggested vital interactions between depressive experiences and gut microbiota metabolism. SCFAs act as essential mediators in the gut-brain axis and might play a vital role in the neurobiological mechanisms of depression [40]. In addition, SCFAs are known to pass through blood brain barrier (BBB), by which SCFAs can modify the metabolism of neurotransmitter in the intracellular signaling pathway [41]. Therefore, SCFAs have been realized to influence the activity of central nervous system (CNS), which may include the cytokine production and/or the modulation of microglial activity [42]. Lower fecal concentrations of the SCFAs butyrate, propionate, and occasionally acetate, have previously been described in patients with severe anorexia nervosa [43]. The anorexia nervosa is one of the most life-threatening eating disorders, which co-arises with other mental illnesses such as anxiety and/or mood disorders [44]. In general, eating disorders are severely damaged mental health conditions that may negatively influence on patients' psychological, physical, and social performance [45]. SCFAs could mediate lipid and/or glucose homeostasis by activating G protein-coupled receptors (GPR), suppressing histone deacetylase (HDAC), which may contribute to the reduction of anti-inflammatory cytokines, resulting in the decrease of inflammation and the improved insulin sensitivity [46]. It has been reported that some of HDACs may be up-regulated in diabetic nephropathy via the modulation of autophagy [47, 48]. In addition, SCFAs are known to alleviate the pathogenesis of nonalcoholic steatohepatitis (NASH) by the activation of AMPK signaling and/or the induction of fatty acid oxidation, which is well-known to be involved in the autophagy [49, 50]. Additionally, it has been shown that SCFAs can

trigger the autophagy in some of cancer cells, which may promote M2 polarization in macrophages [51]. SCFAs-induced cell death seems to be necrotic, which is dependent on the high level of autophagy [52]. Moreover, histone acetylation by SCFAs can increase the production of ROS, which may contribute to the increase of autophagy-related gene expression [53]. Therefore, metabolic parameters including SCFAs should be carefully monitored in patients with depressive disorders. Also, increased attention should be assumed to the patients with depressive symptoms for the early detection of metabolic disorders including hepatic diseases and/or T2DM. Interestingly, it has been reported that a complex interrelationship may exist between SCFAs level and ncRNA profiling in response to intestinal inflammation [54]. In addition, some receptors of SCFAs may be potential targets of regulation by host ncRNAs. Particularly, several miRNAs including miR-132, and miR-329 have been previously found to be altered in various diseases and/or disorders [55].

Gut-brain axis and/or engram theory might be involved in the pathogenesis of psychiatric disorder and/or metabolic syndrome

The gut-brain axis is an intricate, dynamic, and bidirectional communication network between gut and brain. Alterations in the gut-brain axis might be responsible for the development of various metabolic, neuropsychiatric, and/or neurodegenerative disorders. Metabolites including SCFAs could introduce their effects partly via immunological and neuroendocrine mechanisms. Therefore, compositional changes of gut microbiota have been shown to be consequently correlated with the altered function of immunity accompanying an immune and/or of neuropsychiatric disorders [56]. In other words, CNS and the immune system might collaborate on various levels in a body. Interestingly, it has been revealed that a brain possesses the facts of definite inflammation situation such as inflammatory bowel syndrome previously occurred in body, in which the intricate pathology may be controlled by an engrams-activity on brain [57]. This "engram" idea might progress a promising tactic for the treatment of various diseases/disorders with the improvement of gut microbiota [58]. In short, the specific engram may be hold on neuronal assemblies such as in hippocampus, amygdala, and/or cortex, which may functionally link each other to work for an integrated organization managing against various inflammation in body [59]. Shaped by frequent inflammatory conditions, an "engram" might be dedicated to a mild development of those inflammatory diseases. Attractively, it has been presented that unusual instigation of the tryptophan and kynurenine pathway might be involved in the development of various diseases/disorders such as obesity, T2DM, and/or cardiovascular diseases [60, 61]. In addition, the tryptophan and kynurenine pathway have been well-known to be related with depressive and mood disorders, neurodegenerative diseases, and other inflammatory situations including metabolic diseases [62]. Stimulatingly, the kynurenine metabolites might be involved in the regulation of brain memory structure and/or complicated immunity via the modulation of glia/neuron with the probable alteration of "engram". Further consideration of the "engram" concept could lead to the development of amazing prevention/treatments with the modulation of gut microbiota for various troublesome immune-related diseases/disorders [62] (**Figure 2**). Several component molecules involved in the tryptophan and kynurenine pathway may be plausible for the target of dietary intervention, which might be linked to some of immune-related diseases [62]. Indeed, disrupting homeostasis threatens the internal environment in a body, leading to imbalances that can initiate a cascade of health issues, including metabolic disorders and chronic immunity-linked diseases. Because, some of immunity-linked processes might be connected with several neuronal responses to possible "engram" [63]. Some of plausible effects of several inflammatory stressors on "engram" memory formation have been described [57, 64, 65]. Therefore, immune system and CNS might collaborate on some inflammation stages within a body. However, the links of engrams to inflammation may be dependent on several environmental situations [66, 67]. Consequently, "engrams" could recall the inflammatory condition if it opens up again [67]. These engrams made by repetitive inflammation might basically maintain a stable structure whether at rest or performing tasks, however, which has diverse information processing mechanisms under varied conditions [68].

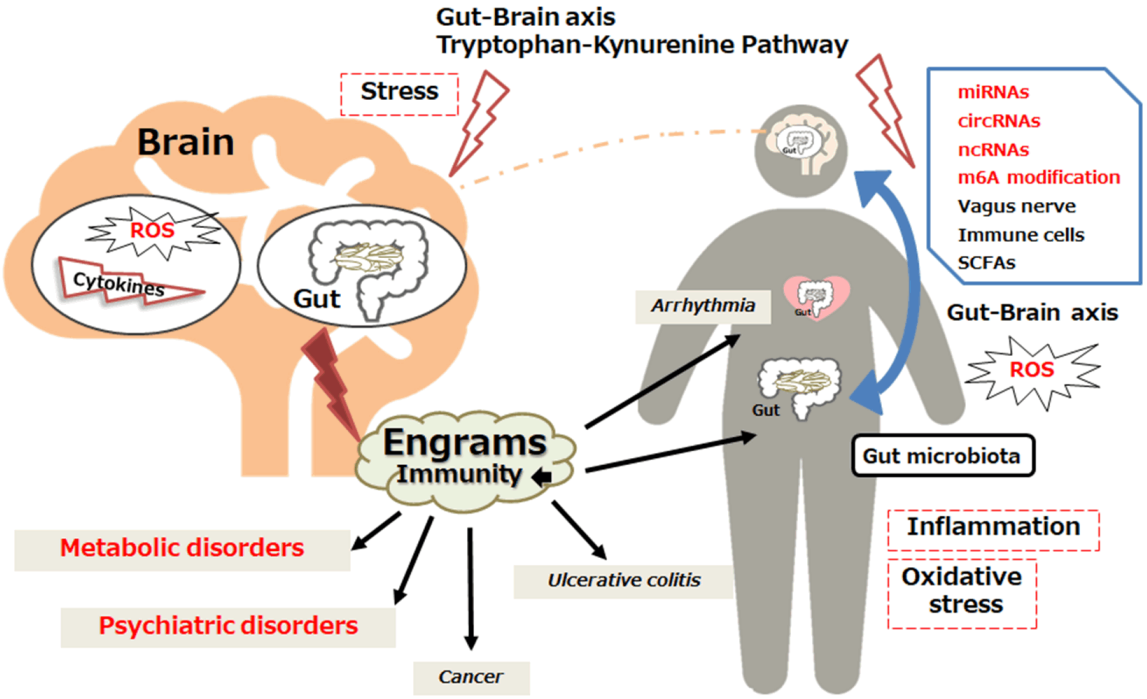

Figure 2. Schematic outline for the pathogenesis of immune-related disorders such as bipolar disorder, major depressive disorder, cardiac arrhythmia, ulcerative colitis, cancer, inflammatory bowel disease, alcohol dependence, and/or metabolic syndrome. The gut-brain axis, with the utilization of ncRNAs, m6A modification, and/or short chain fatty acids (SCFAs), may contribute to the pathogenesis of immune-related diseases via the formation of several "engrams" in the host brain. Inflammation with the production of reactive oxygen species (ROS) might be also involved in the pathway for the modulation of immune cells with the "engrams". Note that some critical cellular activities such as anti-inflammatory reactions and/or cytokine induction have been absent for clarity. "?" means for author speculation.

Remarkably, it has been identified that some immune mechanisms may play an imperative role in promoting liver inflammation in NASH [69]. Indeed, there might be a metabolic predisposition to metabolic syndrome in patients with the psychiatric disorder that is exacerbated by obesity, in which some effects of inflammatory mediators on the brain may consequently contribute to the pathology of these diseases/disorders [70] (**Figure 2**).

Possible treatment tactics with the alteration of gut microbiota against metabolic syndrome and psychiatric disorders

In these ways, gut microbiota may play substantial roles in the development both of metabolic syndrome and psychiatric disorder. Additionally, it has been suggested that the gut microbiota has a strong effect on the epi-transcriptome of ncRNAs [71]. Furthermore, ncRNAs have been suggested to be feasibly worthy biomarkers in various diseases linking to the microbial dysbiosis of gut microbiota [72]. Gut microbiota and/or ncRNA epigenetics could build a complicated cross regulatory network. Hence, some engineering of gut microbiota is becoming a strong tactic for refining human health and/or improving some diseases/disorders, in which the gut microbiota may serve as a therapeutic target. For example, fecal microbiota transplantation (FMT) could considerably repress the metastasis of lung cancer cells, in which the gut microbiota may play a key role via the regulation of several ncRNAs [73]. The gut microbiota has also appeared as a key regulator in the pathogenesis of liver disease, in which the cellular and molecular players may be involved in the cross-talk between the gut microbiota and the liver [74]. The gut-liver axis could provide signals through the gut metabolites as well as hormones that affect metabolism of liver at different levels. Actually, the gut microbiota has a potentially alleviating effect on high-fat diet-induced obesity. Interestingly, alleviating

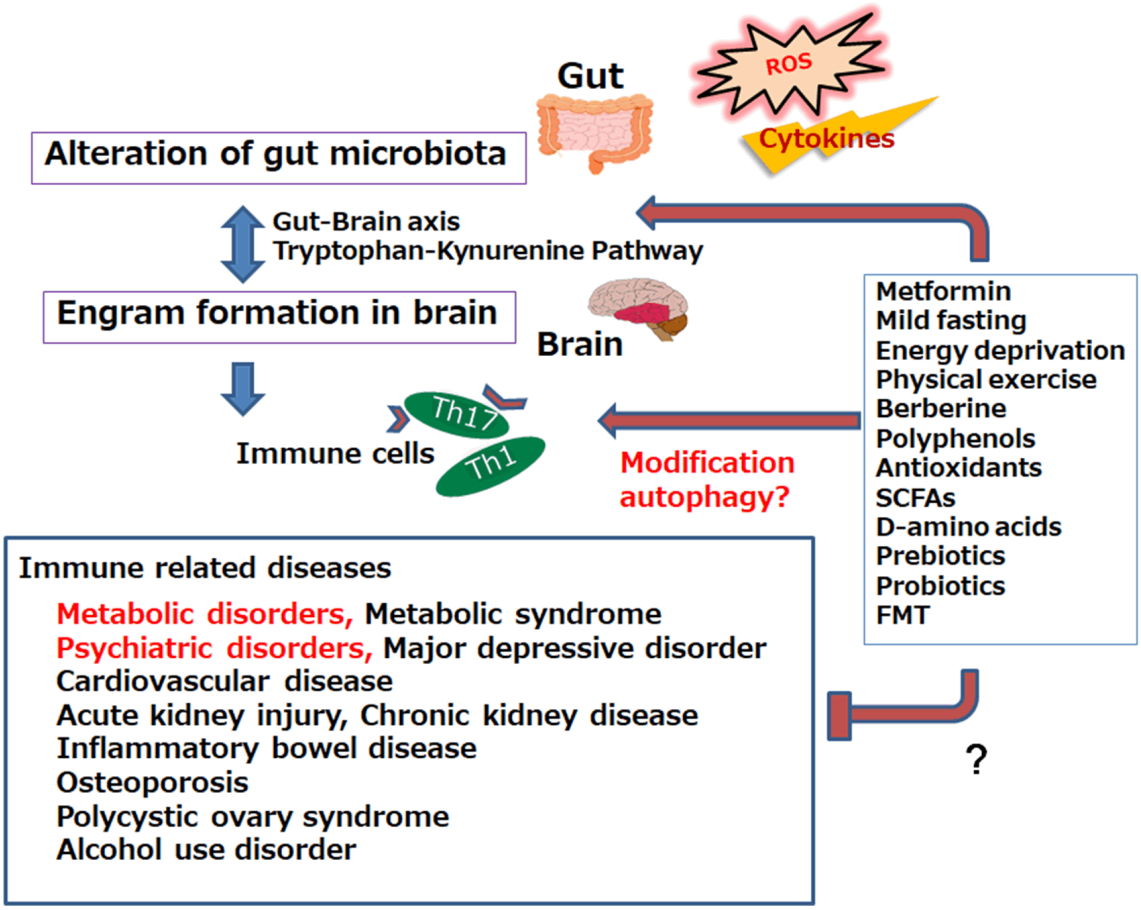

Figure 3. Schematic demonstration of the potential inhibitory tactics against the pathogenesis of immune related diseases including major depressive disorder, alcohol use disorder, and/or metabolic syndrome. Example treatment factors including metformin, berberine, prebiotics, probiotics, and fecal microbiota transplantation (FMT) as well as mild fasting, energy deprivation, and/or physical exercise known to act on the signaling of gut microbiota are also shown, which might be beneficial for the treatment of metabolic syndrome. Note that some of important activities such as cytokine production, inflammatory reaction, and/or reactive oxygen species (ROS) production have been omitted for clarity. "?" means for author speculation.

effects with the FMT may also modify the lipid metabolism of intestine to achieve the resistance to obesity and/or metabolic syndrome [75]. In the happening of host dysbiosis, however, some bacteria and their metabolites might trigger inflammatory pathways in various tissues and/or organs, which could eventually result in exacerbating the whole inflammation of the host [76]. The gene expression could also be changed probably due to the metabolites with the altered microbiome [77]. On the contrary, the gut microbiota from the use of prebiotics and/or FMT can modify and/or improve the host response to various therapeutics including novel immunotherapies [78]. Interestingly, berberine has been known to be valuable against MAFLD via the modification of gut microbiota with the alteration of PI3K/AKT signaling pathway [14, 79]. According to experimental, preclinical and/or clinical findings, therefore, the gut microbiota has been shown to be a striking controller of the gut-liver axis and/or the metabolic diseases. Moreover, microbes in gut could alter the function of CNS through metabolic and/or neuroendocrine pathways, in which the gut-brain axis might be connected for organizing the condition of health and/or disease in the host [80] (**Figure 3**).

As mentioned above, berberine could also modulate the effect of gut-brain axis via the alteration of microglial action on CNS [81]. In addition, it has been described that berberine can amend the DSS-induced colitis by sup-

pressing T helper 17 cell (Th17) immune responses [82]. Moreover, the berberine may also improve metabolic disorders through modulation of the gut-brain axis [83]. Balancing the Th17/regulatory T cells (Tregs) might be an important factor involved in the pathogenesis of DSS-induced ulcerative colitis [84]. Therefore, dysregulation of Th17 cells in the ulcerative colitis might be critical in the injury of gut epithelium [85]. Associations of "engrams" are thought to determine the condition either health or inflammatory disease by arrangements for the Th17/Treg balance. Consequently, the immunological "engrams" could return the primary inflammatory condition, if restarted necessary [66, 86]. Some engrams might worsen the condition of immunological disorders [87]. Depression as well as liver disease, alcohol consumption, stress, and aging processes may disrupt the healthy balance of immune cells with the action of engram. In other words, gut microbiome could regulate the inflammation in the liver as well as in the brain via the alteration of Th17/Treg balance, which can lead to the improvement of liver and/or brain condition, obesity, depression, and metabolic syndrome (**Figure 3**).

Another imaginable way for therapeutic intervention against metabolic syndrome, synaptic removal achieved by microglia could introduce a lack of bad memories with engram cells [88]. It has been reported that microglia are connected to the rate of synaptic density, memory, and/or learning [89]. In addition, there are remarkable associations between gut microbiota and demyelination via the microglia in CNS, suggesting that the crosstalk of gut microbiota and microglia might play a significant role for the clearance of engrams [90]. Alterations in the composition of gut pathological microbiota with the failure of engrams clearance may also be linked to gut dysbiosis for the exacerbation of certain inflammations in the host [91]. Remarkably, a pleiotropic drug metformin could improve the metabolic process within gut microbiome [92]. Similarly, a dietary approach may amend the gut microbiota that are potentially beneficial for the treatment of metabolic disease, immunological and/or neurodegenerative disorders [93]. Improved gut microbiota could further inhibit the production of ROS in order to keep the health of liver and brain in the host [94], which might also be important for the neuro-regeneration by neuronal stem cells and/or glial cells [95-97].

Inflammatory factors, oxidative stress, and/or the alteration of microglia may totally limit neuroplasticity in CNS [98]. In addition, the gut microbiome has been known as a potential significant factor for the kynurenine metabolism [99]. Some microbial depletion could reduce the kynurenine metabolism in the peripheral nerves [100]. Remarkably, application of the tryptophan and kynurenine metabolism can improve the gut microbiome [101]. Prebiotics/probiotics may affect the kynurenine metabolism [102]. For example, some probiotics may decrease the kynurenine concentration in the serum of patients with major depressive disorder, which could improve the cognitive function of patients [103]. Another probiotics could also reduce the metabolism from tryptophan to kynurenine with potential antidepressant properties in rat models [104, 105]. Again, disrupting homeostasis of gut may intimidate the internal environment in a body directing to imbalances that can introduce a lot of health issues [62, 101]. Remarkably, we presume that metabolic diseases, psychiatric disorders, cardiovascular disease, osteoporosis, neurodegenerative disease, and other immune-related diseases might similarly relate to the pathogenesis that might be grounded on the engram memory system [93, 106, 107]. Future work should direct to the anti-inflammatory effects of gut microbiota on the host immune cells with the gut-brain axis.

Future perspectives

In total, the presence of certain pathophysiological mechanisms is suggested in metabolic syndrome, which may be linked to psychiatric depressive symptomatology. Therefore, treatments should be beneficial for metabolic syndrome patients with interventions of gut microbiota promoting healthy lifestyle and physical activity as well as for psychiatric disorders. Vigorous research might provide insights into dynamic interactions between gut microbiota and immunity during the development of metabolic syndrome. In particular, chronic inflammation related to the formation of engrams memory seems to be a key factor for the pathogenesis of metabolic syndrome. Therefore, clearing the bad memory of "engrams" might be

favorable for the prevention and/or treatment of metabolic syndrome. Is it possible to eliminate the memory of engrams without any brain damages? We consider this is the significant point for the therapeutic interventions. Information of alterations in the gut microbiota could be transmitted by the sympathetic vagal afferent nerve to the CNS, which in turn could modify the response of engrams via the microglial action. In fact, probiotics have a therapeutic effect on the regulation of chronic inflammation in inflammatory bowel disease [108]. This might be the point for the therapeutic interventions beneficial to the immunological disorders. On the other hand, the devastation of the good homeostasis in the gut-brain axis could lead to cognitive impairment and memory decline [109].

Nowadays, the metabolic diseases are increasing due to the rise of fast-food consumption as a result of high-sugar and high-fat diets. However, dietary polyphenols may interact with gut microbiota to produce some valuable metabolites that can regulate appetite enhancing prebiotic effects [110]. The possible modulation of gut microbiota may be associated with an improvement in the risk factors of metabolic syndrome triggered by the high-sugar and high-fat diets [111]. Interestingly, the presence of D-amino acids has been shown to be linked to the protection of several organs against irritable bowel syndrome [112]. D-amino acids are the enantiomeric counterparts of L-amino acids, which could play key roles in cellular physiology against oxidative stresses. In general, some dietary intake could contribute to the production of several metabolites including D-amino acids by the fermentation in the gut microbiota. Accumulating evidence suggests that alterations in the gut microbiota-derived metabolites including SCFAs and/or D-amino acids may play a key role in the pathology of depression via the gut-brain axis and immune systems [113]. Altered levels of SCFAs, D-amino acids, and ROS levels in the gut have been shown to be relevant to the pathogenesis of the diabetic nephropathy [114]. D-amino acids have been studied as a potential treatment for metabolic disorders. For example, D-serine may play a physiologic role in both appetite and insulin regulation in the pancreas, which may be associated with considerable weight gain and/or metabolic disorders [115]. However, further exploration for the comprehension of gut-brain axis may be compulsory for the development of superior therapeutic application against psychiatric disorders. In particular, the potential of microbiome-targeted diet strategies should be furthermore explored.

Conclusion

Several metabolites and ncRNAs could be involved in the development of metabolic syndrome and psychiatric disorders, in which the association among gut, liver and brain may play an important role with brain engrams. In addition, the connection between brain and immunity might also influence the development of these disorders. An in-depth knowledge of the role of gut-liver-brain axis may be valuable for the development of novel clinical diagnosis and treatment tactics for these disorders.

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Disclosure of conflict of interest

None.

Abbreviations

BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; circRNA, circular RNA; FFAR2, free fatty acid receptors 2; FFAR3, free fatty acid receptors 3; FMT, fecal microbiota transplantation; GPR, G protein-coupled receptors; HDAC, histone deacetylase; lncRNAs, long non-coding RNAs; MAFLD, metabolic disorder-associated fatty liver disease; mRNA, messenger RNA; miRNA, microRNA; NASH, nonalcoholic steatohepatitis; ncRNA, non-coding RNA; QOL, quality of life; ROS, reactive oxygen species; SCFA, short-chain fatty acid; siRNA, short interference RNA; T2DM, type 2 diabetes mellitus; Th17, T helper 17 cell; Treg, regulatory T cells; UTR, untranslated region.

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