Associations between Gut Microbiota, Immunity and CNS

Subjects: Biotechnology & Applied Microbiology

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Nerve cell death accounts for various neurodegenerative disorders, in which altered immunity to the integrated central nervous system (CNS) might have destructive consequences. This undesirable immune response often affects the progressive neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, schizophrenia and/or amyotrophic lateral sclerosis (ALS). It has been shown that commensal gut microbiota could influence the brain and/or several machineries of immune function. In other words, neurodegenerative disorders may be connected to the gut–brain–immune correlational system. The engrams in the brain could retain the information of a certain inflammation in the body which might be involved in the pathogenesis of neurodegenerative disorders. Tactics involving the use of probiotics and/or fecal microbiota transplantation (FMT) are now evolving as the most promising and/or valuable for the modification of the gut–brain–immune axis.

gut microbiota engram neurodegenerative disorders Alzheimer's disease Parkinson's disease amyotrophic lateral sclerosis schizophrenia inflammation reactive oxygen species

1. Introduction

Neurodegenerative disorders are the most common factors of disability, which refer to the gradual decrease in function of the nerves of sensory, motor, and mental activity subsequent to the death of several neurons [1]. The nerve cell death accounts for the various neurological dysregulations of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, schizophrenia and amyotrophic lateral sclerosis (ALS) [2][3][4][5]. Similarly, some cases of autism and depression also result from nerve cell death [6][7][8]. Precise insight into the pathology of these diseases still remains elusive. Oxidative stress is defined as a condition of metabolic dysfunction facilitated by the discrepancy between the elevated production of reactive oxygen species (ROS) and the antioxidant defense activity in a body [9]. In one sense, a conceivable pathophysiology of neurodegenerative disorders might be recognized by the increased oxidative stress. For example, the elevated production of ROS has been hypothesized to play a key role in the development and poor outcome of schizophrenia patients [10]. Oxidative stress may also be increased in ALS patients, which may affect the mitochondrial dysfunction eventually leading to nerve cell damage and/or neuronal loss [11]. In particular, mitochondrial homeostasis is critical to maintain neuronal function and mitochondrial dysfunction is connected to neurodegeneration [12]. Neurons and glial cells are typically vulnerable to excess ROS because of comparatively insufficient antioxidant capabilities, which may increase vulnerability to

neuronal damage and functional deficits [13]. It has been shown that these related mitochondrial disruptions of the oxidative pathways, several inflammatory cytokines, excess amounts of ROS, and altered microglia activities may bring harmful results to the process of nerve cell degeneration that eventually leads to nerve cell death [14] (**Figure 1**).

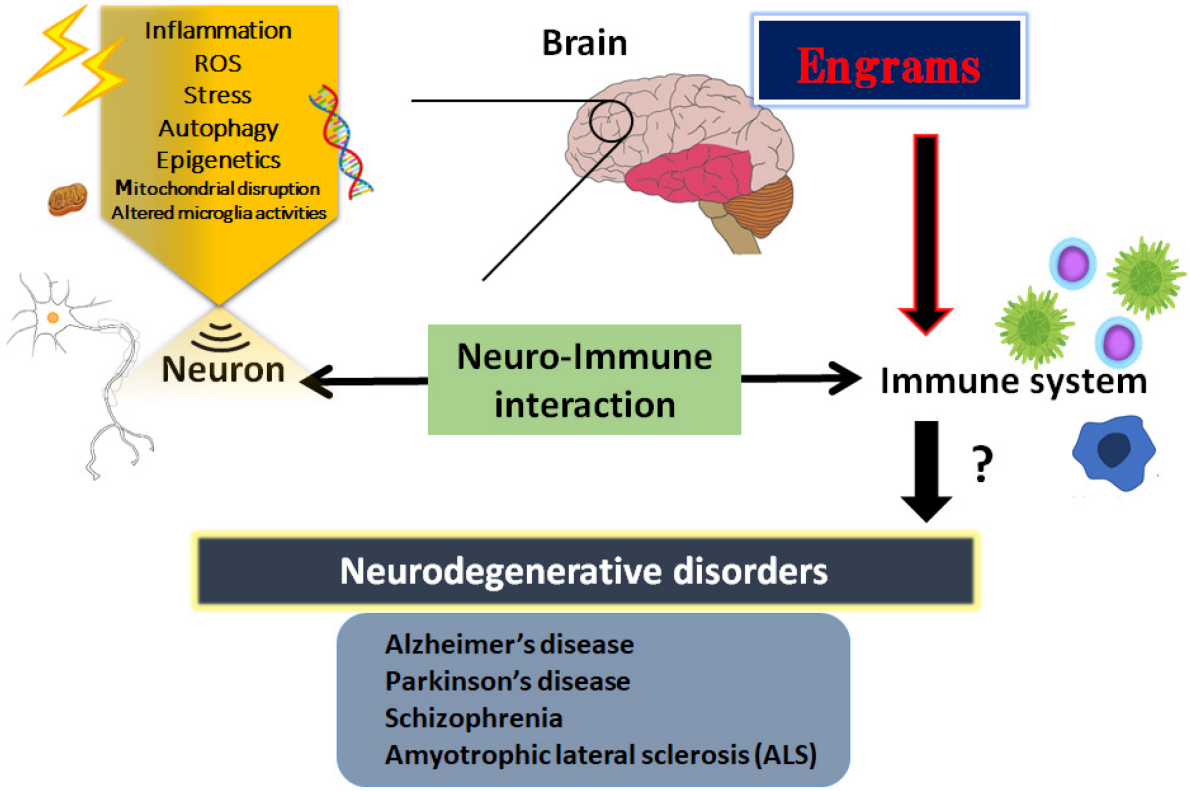

Figure 1. Schematic illustration shows an introduction to the essential role of neuro-immune interaction in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and schizophrenia. The immunity could generally communicate with the brain or CNS. Illustration of the involvement for the pathogenic roles of various stresses, inflammation, ROS, epigenetics, and engrams is shown. Note that several significant items have been omitted for clarity. Abbreviation: CNS, central nervous system; ROS, reactive oxygen species.

Increasing evidence indicates the complicated associations between gut microbiota, immunity and the central nervous system (CNS) [15]. Additionally, a variety of studies have shown the potential association between gut microbiota and neurodegenerative disorders including depression, autism, schizophrenia and Parkinson's disease [16]. While regular gut microbiota could defend the CNS, the dysbiosis of microbiota might aggravate neurodegenerative and/or mental health disorders [17].

2. Inflammatory Neuro-Immune Responses

Inflammatory progression has a key role in various cellular processes and is suggested as the pathogenesis of neurodegenerative disorders [18]. Consistently, it has been revealed that neuro-inflammation triggered by bacterial

or viral infections could induce schizophrenia in animal models [19]. In addition, it has been described as a reciprocal functional mechanism between the immune system and CNS [20]. For example, immune cells could modulate behavior and cognition of the host by direct interactions with the CNS [21]. A low-grade neuro-immune/inflammatory response is essential to keep the neurogenesis and/or the homeostasis of brain [5][7][22], suggesting that mild transient immune response might be employed as a restorative role in CNS. Consequently, an array of neuro-immune aberrations related to the chronic activated inflammatory reaction have been identified in patients with neurodegenerative disorders including schizophrenia [22]. Generally, an elevated level of inflammation markers in the blood and/or in cerebrospinal fluid (CSF) of the CNS has been detected in patients with neurodegenerative disorders [23]. Therefore, prospective treatment with anti-inflammatory medication has been suggested as a secondary treatment in patients with neurodegenerative disorders including schizophrenia or ALS [24]. It has been shown that extra prolonged stresses may be a robust risk factor for the development of some psychiatric diseases with a reduced number of mitochondria in the cortex [25].

Inflammatory oxidative stress may produce an excess amount of ROS which could be characterized as oxygen-comprising small molecules prone to react with several biological materials such as DNA [26]. In addition, an excess amount of ROS production could initiate an activation of autophagy in cells, suggesting an essential role for ROS in the activation of autophagy [27]. Generally, autophagy would play a protective role in cells; however, autophagy is also related to apoptotic cell death or necrosis in certain conditions. Additionally, autophagy could regulate the levels of several inflammations [28]. Hence, autophagy might be involved in the pathogenesis of neurodegenerative disorders. The significant effect of autophagy may be determined by the type of stimulus, cell types, the microenvironment, and/or other biological factors [29]. In intracellular signaling pathways, autophagy could be stimulated by the activated AMP-activated protein kinase (AMPK) during the situation of energy deficit in cells [30]. The activity of AMPK is also critical in the cells of the CNS for preserving neuronal integrity and for neuron survival against an excess amount of oxidative stresses [31].

3. Engrams and Neuro-Immune Responses in the Pathogenesis of Neurodegenerative Disorders

The CNS and the immune system might collaborate on various levels in a body; however, the mechanisms of holding the specific immune-challenge have remained vague. Very lately, it has been clearly shown that the brain keeps the facts of certain inflammation such as inflammatory bowel syndrome occurred in the body [32]. This specific memory seems to be an immunological remembrance called “engrams” [33]. Here, the researchers would like to use this word “engrams” as the meaning of immunological remembrance *matching to the meaning of “memory-traces”.* The concept of engrams has been fairly hypothetical for the basic units of memory. Now, neuronal assemblies that hold the specific disease engrams have been known in the amygdala, hippocampus, and/or cortex, which may suggest that engrams are distributed among multiple brain regions functionally linking each other as an integrated engrams organization [34]. Associations of these engrams are thought to determine the situation of the host, either of health or disease, by engram arrangements, which may be frequently dependent on several environmental conditions [35]. Consequently, the immunological engrams could restore the initial

inflammatory disease condition, if rebooted [33]. Created by stressful and/or repetitive inflammatory occasions, the engrams might commit to a slow progression of chronic diseases including neurodegenerative disorders [36]. Epigenetic changes such as DNA methylation or acetylation within the cells of the neuronal assemblies might be important mechanisms of the engram formation [37], which is also a significant factor for the fine-tuning of the function in the healthy brain [38]. Epigenetics may also stabilize engrams for the effective recovery of fear memory [39]. Therefore, engrams and/or epigenetic changes could be related to the immune consequences in the pathogenesis of various neurodegenerative disorders [40] (**Figure 1**). The synergistic arrangement of engrams might bring in the solid progression of several diseases, which involves the concept that any complex neurological and/or immunological consequences could result from the interaction of these engrams with immunity. Additionally, frequent subtle immune challenges might result in the stable formation of multiple engrams positioning independent information [41]. Synaptic variations might validate the specific development of engrams during memorizing for supporting memory. Maintenance of the memory might be achieved by a meta-plasticity mechanism that raises the change in neurons within an engram, which may be further encouraged by epigenetic regulators such as histone deacetylases (HDACs) [42]. In fact, the HDACs-related signaling pathways have been significantly associated with the alternative expression of several genes related to neurodegenerative disorders [43]. Consistently, some kinds of epigenetic regulators modified by environmental factors have been suggested as playing a crucial role in the pathogenesis of various neurodegenerative disorders [44]. In short, the brain could hold several specific inflammatory responses as information of pathological neuronal images called “engrams”. This concept could correctly elucidate the pathogenesis of various neurodegenerative disorders and the related CNS disorders, which might contribute to establishing a new strategy for the therapeutic interventions.

4. How to Modulate the Engrams

Some engrams could potentially trigger and/or exacerbate the conditions of neurodegenerative disorders [45]. Therefore, clearing the bad memory of “engrams” might be favorable for the prevention and/or treatment of neurodegenerative disorders. In the experiment of dextran sulfate sodium-induced colitis, the authors applied the chemo-genetic procedure of the designer receptor exclusively activated by designer drugs (DREADD) system for the inhibition of engram activity [32]. However, it seems to be impossible to currently use this system in the clinical treatment of humans. Now, is it possible to clear the memory of engrams without neuronal cell death and/or any brain damage? This is the point for therapeutic interventions. In one possible way, synaptic removal could be achieved by microglia capable of initiating the oblivion of memories with engram cells [46]. It is considered that microglia can make synapse elimination a mechanism for forgetting memory retentions [46]. In addition, it has been reported that microglia are related to synapse density, learning, and/or memory [47]. There are significant associations between gut microbiota and demyelination by the microglia in the brain, suggesting that the crosstalk of gut-microbiota and brain-microglia might play a key role for the clearance of engrams [48]. It has been shown that regulation of the microbiota might be connected to the possible therapies of neurodegenerative disorders [49]. A gut–brain axis indicates a bidirectional connection between gut microbiota and brain, which is a vital assembly in the pathophysiology of several neurodegenerative disorders [50]. This concept might include the associations between gut microbiota and more broad CNS disorders. For example, it has been shown that the composition of

gut microbiota might be associated with narcolepsy type 1 [51]. Changes in the conformation of gut microbiota may be accepted by the sympathetic vagal afferent nerve transmitting to the CNS via the microglial action, which in turn could produce and/or modulate the responses of engrams. Studies have proven that some species of bacteria could produce catecholamines and/or acetylcholine, which might contribute to the responses of the sympathetic nerve [52].

5. Utilization of Gut–Brain Axis for the Treatment of Neurodegenerative Disorders

The dynamic residency of microbes in the gut may play a fundamental role in managing host physiology. In addition, recent advances have emphasized the significance of gut microbiota in neurodevelopment with considerable associations with the onset and/or the progression of neurodegenerative disorders [53][54]. Furthermore, it has been shown that the dysbiosis of gut microbiota might worsen the symptoms of various neurodegenerative disorders [55]. Alterations in the composition of gut microbiota, termed gut dysbiosis, with an increased number of potentially pathological organisms might play a prominent role in the pathogenesis of CNS-related disorders. For example, ALS patients may often demonstrate some changes in their gut microbial communities compared to the paired healthy controls [56]. Furthermore, increasing gut dysbiosis has been shown to worsen the symptoms with ALS [57]. Evolving evidence also connects the gut dysbiosis to the exacerbation of impaired autophagy in the immune-mediated chronic neuroinflammation [58]. Interestingly, it has been reported that a pleiotropic drug modulating AMPK and/or autophagy signaling, such as metformin, could alter the gut microbiota and its metabolic processes [59]. Consequently, dietary approach to alter the gut microbiota could be advantageous for the treatment of neurodegenerative disorders [60]. Gut microbiota could regulate and/or inhibit the production of ROS to retain the host's brain health [61]. It might be important to diminish the levels of ROS for neuroregeneration with neuronal stem cells [62][63]. In addition to the unfavorable effects for the stem cells, ROS might skew the function of microglia with the oxidized mitochondria in glial cells (**Figure 1**) [64]. Inflammatory factors, oxidative stress, and/or the alteration of microglia are known to limit neuroplasticity in the CNS [65]. In these ways, certain gut microbiota with the inhibition of ROS could probably prevent the incidence and/or attenuate the symptoms of neurodegenerative disorders by regulating the production of ROS and by clearing engram memory via the alteration of functional microglia in the brain (**Figure 2**).

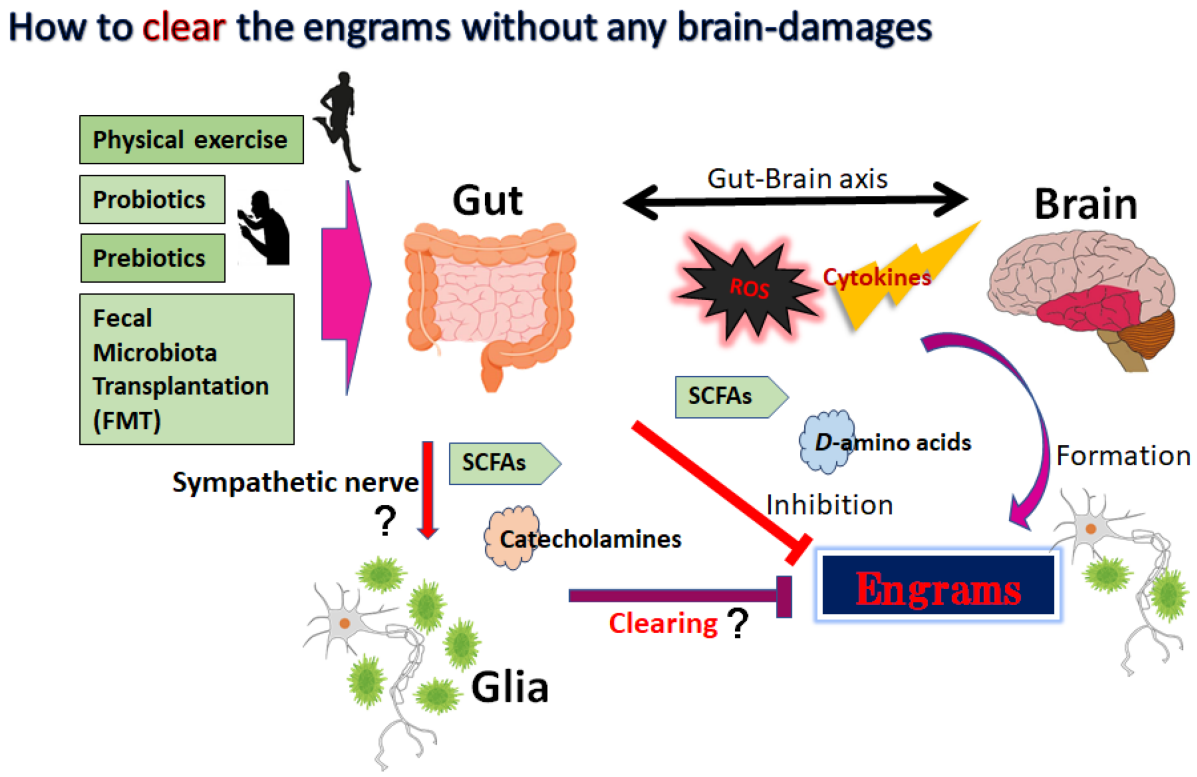

Figure 2. The gut microbiota could support favorable action against disease progression of neurodegenerative disorders by affecting the engrams and/or brain–immune axis, which may include the inhibition or production of cytokines, ROS, SCFAs, certain D-amino acids, and catecholamines. Mild physical exercise, probiotics, prebiotics, and fecal microbiota transplantation (FMT) might potentially be more successful than conventional symptomatic therapy for the treatment of neurodegenerative disorders. Arrowhead indicates stimulation whereas hammerhead shows inhibition. Note that several important activities such as cytokine induction or anti-inflammatory reaction have been omitted for clarity. Abbreviations: FMT, fecal microbiota transplantation; SCFAs, short-chain fatty acids; ROS, reactive oxygen species.

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