The Microbiota–Gut–Brain Axis

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The microbiota–gut system can be thought of as a single unit that interacts with the brain via the “two-way” microbiota–gut–brain axis. Through this axis, a constant interplay mediated by the several products originating from the microbiota guarantees the physiological development and shaping of the gut and the brain. The modification of the composition of the microbiota destroys the bottom-to-top communication that ultimately influences brain motor, sensory, and cognitive functions, maintains brain homeostasis and/or contributes to the onset of pathological conditions. Elucidating the interplay between the gut microbiota and the central nervous system, and the role of microbiota in neuroinflammation, will lead to a better understanding of many neurodegenerative diseases pathogeneses, and, hopefully, to the development of new preventing or therapeutic strategies.

Keywords: amyloid-β ; endotoxin ; short chain fatty acids ; cytokines ; neurovascular unit ; vagus nerve

Cover Legend

Schematic representation of the bottom-to-top regulation of neuroinflammation in Alzheimer Disease (AD) pathogenesis. (**Left panel**) In healthy conditions, the microbiota–gut–brain axis modulates key processes, including immune cell maturation and maintenance of the gut epithelium. Short chain fatty acids (SCFAs) produced by the gut microbiota cross the Intestinal Barrier (IB) and, via the circulatory system, reach and cross the blood–brain barrier (BBB). Once in the brain parenchyma, SCFAs target microglia and regulate their functions. The gut microbiota is one of the main producers of Aß peptide and lipopolysaccharides (LPS), which integrate in chylomicrons (CM) and cross the BBB. Aß is readily retro transported to the circulatory system for its disposal. Blue lines represent known beneficial pathways of microbiota. (**Right panel**) Microbiota overproduction of LPS and cytokines causes modification of the permeability of the gut epithelium, of the neurovascular unit (NVU) and of the glymphatic system. Gut microbiota production of SCFAs is reduced in AD, while the production of proinflammatory cytokines, including IL-1, IL-6, and TNF-α, as well as microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs), is increased. These factors translocate to the brain where they modulate microglia via Toll-like Receptor 4 (TLR4), and activated M1 microglia release IL-1, TNF-α, reactive oxygen species (ROS), and nitric oxide (NO) that cause neuronal damage. In addition, proinflammatory cytokines cause activation of astrocytes (A1), which release cytokines that in turn decrease aquaporin-4 (AQP4) expression and modify NVU permeability. Peripheral Th1, activated by isoleucine (Ile) and phenylalanine (Phe) produced by microbiota, can recognize the bacterial metabolites or MAMPs and migrate to the brain via the damaged BBB. Aß peptide produced by the microbiota can easily cross the IB or be retrogradely transported to the brain via the vagus nerve. Since disposal of Aß peptide is impaired by the damage to the BBB, Aß peptide precipitates to form plaques, which further worsens microgliosis and astrogliosis, increasing the severity of AD pathology. Red lines indicate the bottom-to-top damaging pathways so far demonstrated.

1. Introduction

The gut and its microbiota represent the largest absorption organ, and the largest reservoir of microbes in the human body, respectively. The microbiota consists of almost 10^{14} microorganisms that are mainly bacteria. These are the Gram-positive *Firmicutes* (51% of the population), most of which are *Lactobacilli*, and the Gram-negative *Bacteroidetes* (48%). Physiologically and pathologically the gut and its microbiota can be considered a single system (microbiota–gut), whose interactions give rise to responses that affect the functions in organs and systems of the whole organism. Among the systems involved, the central nervous system (CNS) is in constant communication with the microbiota–gut, through the “two-way” microbiota–gut–brain axis. This interaction involves distant and local networks through neural, immunological, metabolic, and hormonal signaling pathways [1], thus dysfunction at every level of the axis may affect all the other components. It has been shown that brain diseases alter the neurochemistry of the enteric nervous systems (ENS), the functioning of the immune system (IS), and the microbiota itself, using top-to-bottom directional pathways [2][3][4]. In addition, several bottom-to-top directional pathways, activated by microbiota products, are necessary for the correct

development and physiological functioning of the brain [5]. Changes in the microbiota composition, the dysbiosis, contribute to several neurodegenerative disorders such as Alzheimer disease (AD) [2][5][6][7][8], Parkinson's disease (PD) [9], multiple sclerosis (MS) [10], and amyotrophic lateral sclerosis [11].

The focus of the present Encyclopedia entry will be on the role that microbiota products have on astrocytes and microglia to guarantee an adequate environmental milieu for neuronal activity. When subjected to pathological stimuli, such as those deriving from an altered microbiota, both glia cell types can shift their activation profiles from a healthy to a diseased state, triggering neuroinflammatory mechanisms that cause neurodegenerative effects.

2. The Microbiota–Gut–Brain Axis and Alzheimer Disease

2.1. The Dysbiosis and the Alzheimer Disease

Increased lifespan has resulted in the increased frequency of age-related diseases, including AD, the most common type of dementia, which accounts for more than 65% of all dementia cases. AD currently affects approximately 40 millions of elderly subjects in Western countries. The increased life expectancy in the world population has seen a progressive increment of this type of dementia, which is expected to triplicate in incidence by 2050. Indeed, beyond the familial forms of AD, of relatively early onset, the idiopathic and most common forms of AD have late onset and are often indicated with the acronym LOAD (late onset AD). AD is a neurodegenerative pathology characterized by a slow, irreversible decline in the cognitive functions that affects different brain regions. To date, very few effective pharmacologic agents that prevent or slow down the disease progression are available.

Since 2010 it was raised the question as to whether AD depends on aging or, whether the late age allows the disease to clinically manifest as the result of the accumulation of stress factors throughout lifetime [12]. Among the identified factors, the alterations in the gut microbiota, and the subsequent inflammatory processes, have been considered responsible for the appearance of neurodegeneration 15–20 years later [13][14].

2.2. The Microbiota and the Central Nervous System Glial Cells Interplay in Alzheimer Disease

The contribution of the different bacterial strains to the integrity and dysfunction of the microbiota–gut–brain axis is not completely known.

Some brain areas, such as the cortex, hippocampus, and amygdala, are particularly susceptible to the products of the microbiota [5], and these areas correspond to those primarily altered in AD. Although brain diseases were traditionally attributed solely to the malfunctioning of neurons, it is becoming more and more evident that proper interplays among neurons, astrocytes, microglia with peripherally derived cells and molecules are of fundamental importance for the physio-pathological organization of the brain [15]. Nevertheless, recently a fourth actor has come into focus, the microbiota, which releases factors that are fundamental for the physiological functionality of astrocytes and microglia. Alterations of the microbiota can reverberate on the cells of the CNS, and particularly on the astrocytes and microglia, modifying their functions. Much remains to be explored regarding the involvement of the different microbial taxa, of other peripherally derived cells, and of molecules that regulate the microglia and astrocyte functions. Microglia and astrocytes can have simultaneously multiple profiles of activation, which can represent the extremes of a continuous spectrum of reactive profiles [16]. The mechanisms regulating their diverse functional properties remain unknown, but evidence suggests that environmental cues, such as those deriving from the microbiota, are important not only in physiological conditions, but also in many neurodegenerative diseases such as AD. Interestingly, the administration of sodium oligomannate (GV-971), a mixture of oligosaccharides, has been shown to reduce the levels of microbiota-derived amino acids in the blood and brain of AD animal models, and to promote a consistent cognition improvement in mild-to-moderate AD in humans [17]. In 2020, the U.S. Food and Drug Administration (FDA) gave a formal nod to commence a Phase III clinical trial in the United States to test the probiotiv GV-971 on patients with AD.

The disruption of the Blood Brain Barrier (BBB), Neurovascular Unit (NVU) and of the glymphatic system causes a reduction in the transport and inefficient removal of toxic substances, which can accumulate in the brain parenchyma, implementing a vicious circle of neuroinflammation and tissue damage [18][19][20][21][22][23]. Since the glymphatic system facilitates the clearance of interstitial Aß and tau [24], the impairment of all these mechanisms decreases Aß clearance [25][26][27], increasing Aß extracellular levels. The modifications of astrocytes functionality, caused by dysbiosis, are responsible for microlesions of the NVU and of the glymphatic system, decreasing the disposal of Aß peptides in the brain parenchyma, and increasing the risk of amyloid plaque formation [24].

Furthermore, it has been demonstrated that signals from the microbiota delineate microglia morphology and functionality, and dysbiosis causes microglia dysfunctionality. Erny and coworkers [28] demonstrated that the microbiota is important for the maturation and maintenance of microglia in proper steady-state physiological conditions, ready to display a rapid response to damaging stimuli. An emerging hypothesis is that the microbiota influences AD pathology, increasing Aß production in the gut, which may cause increased Aß deposition in the brain, Aß plaque formation and activation of microglia. The activated microglia migrate to the sites of Aß plaques, interact with Aß deposits and regulate Aß levels in the brain [29][30].

2.3. New Advanced Methodologies to Study the Microbiota-Gut-Brain Axis

Human-induced pluripotent stem cell (iPSC) technology, a recent bioengineering technique, is considered a promising methodology to reproduce in vitro complex systems such as the microbiota–gut–brain and to interconnect them. Further, iPSC can be utilized to differentiate all major brain cell types to study many neurodegenerative diseases [31][32][33]. Using iPSC-derived cells from normal and diseased patients, it is now possible to understand the complex cellular/molecular interplay that occurs between the different brain cell types in AD. It can be envisaged that this new technology can be of importance to understand the complex communication between the microbiota and brain cells, recapitulating the bottom-to-top directional pathways in a simpler system that can even be used to generate organoids that mimic native brains [32].

A special mention is deserved to the MINERVA platform (MIcrobiota–Gut–BraiN EngineeRed platform for eVAluating the impact of intestinal microflora on brain function) founded by the European Research Council (ERC) [34]. MINERVA is designed to allow researchers to develop therapeutic strategies using a personalized medicine approach. A deeper knowledge of microbiota–gut–brain interactions may lead to new therapeutic approaches through which neuroinflammation/neurodegeneration can be dampened, acting indirectly through the microbiota–gut–brain axis.

3. Conclusions

We have summarized the role of the microbiota–gut–brain axis as an integral part of the pathogenesis of AD. Indeed, the “two-way” interactions among the intestinal microbiota, the peripheral immune system, and the CNS are essential for the maintenance of the host health, and their dysregulation can be one of the initiating factors in multifactorial chronic neuroinflammatory diseases, such as AD. Neuronal pathways, hormones, microbial molecules, and metabolites are all involved in the signaling between these two regions. Although the causes of AD are still not clear, and no curative treatments are available, the experimental and clinical data collected strongly address the research versus preventive approaches aimed at reducing Aβ production and/or inhibiting the self-assembly of amyloidogenic peptides, as shown by the recent, although controversial, approval of aducanumab [35]. The modification of the composition of the microbiota destroys the bottom-to-top communication that ultimately influences brain motor, sensory, and cognitive functions, maintains brain homeostasis and/or contributes to the onset of pathological conditions. Elucidating the interplay between the gut microbiota and the central nervous system, and the role of the microbiota in neuroinflammation, will lead to a better understanding of many neurodegenerative diseases pathogeneses, and, hopefully, to the development of new preventing or therapeutic strategies.

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