Probiotics, prebiotics and their role in Alzheimer's disease

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Accumulation of amyloid and dysfunctional tau proteins in the brain, along with the development of dementia, characterizes Alzheimer's disease (AD). Although the cause of AD is currently unknown, it has been shown that the onset of the disease, with amyloid-beta peptide (Aβ) accumulation, occurs 10–20 years before the development of the clinical signs; to date, several factors, including lifestyle habits (such as diet and exercise), chronic infection and inflammation, have been related to AD pathogenesis and progression (Sochocka et al., 2019). In addition, the gut microbial dysbiosis seems to be a critical feature able to characterize AD and regulate Aβ production. Indeed, imbalances in gut microbiota can induce aberrant immune responses which, in turn, can disrupt the local and systemic homeostasis of the host (**Figure 1A**). Moreover, it has been proposed that the gut microbiota, represented by intestinal microflora, may participate in the development of the disease through a network called "gut-brain axis," that is a bidirectional signaling mechanism between the central nervous system and the intestinal tract. Gut has the largest nervous system, outside the central nervous system, that is in close interplay with the microbiome (MB), the other human genome. The extraordinary complexity of the intestinal ecosystem is represented by more than 100 trillion of microbial cells and their interaction with the intestinal epithelium can influence brain functionality and behavior. Likely, human MB is a promising target for prevention and therapeutic interventions. Indeed, several approaches have been employed with the aim to reduce age-related dysbiosis in both experimental model and in clinical studies. These include strategies to regulate MB via the administration of probiotics and prebiotics, and dietary interventions. The progress of research on the role of intestinal MB in the development of AD will dictate the future for the employment of pro- and prebiotics in the prevention/treatment of AD (D'Argenio and Sarnataro, 2019).

First, we have to understand "when and how intestinal bacteria promote AD?"

Because of the existence of the "gut-brain axis" via immune, neuroendocrine and direct nerve mechanisms, changes in the intestinal microflora have been associated to various neurodegenerative diseases (D'Argenio and Sarnataro, 2019), with possible involvement in AD. Interestingly, studies comparing the microbiota of AD cases respect to that of healthy, control patients, showed that the microbial diversity was reduced in AD patients with a decrease in the number of Firmicutes and an increase in the percentage of Bacteroidetes (Vogt et al., 2017) and Proteobacteria (Liu et al., 2019).

Moreover, bacterial infections can also cause AD. Chronic Helicobacter pylori infection has been shown to increase Aβ levels in the plasma of AD patients and to induce, *in vitro*, hyperphosphorylation of tau by activation of glycogen-3β synthase kinase (GSK3β; Wang et al., 2015).

Finally, bacterial amyloids have been shown to activate signaling pathways that underlie neuropathology of AD, and study carried out using APPPS1 transgenic mice in the absence of the gut microbiota (D'Argenio and Sarnataro, 2019) reported a reduction in amyloid accumulation, indicating a direct link between MB and amyloid.

Some bacteria, such as Salmonella enterica, Mycobacterium tuberculosis, Staphylococcus aureus, Bacillus subtilis, and E. coli, are able to produce amyloid peptides, which behaves like seeds for the aggregation of amyloid in the brain and act by increasing the nucleation of Aβ aggregates (Zhou et al., 2012) triggering an inflammatory response. MB participates in the expansion of the neuroinflammation associated to the production of amyloid (D'Argenio and Sarnataro, 2019). It has been shown that metabolites released from pro-inflammatory bacteria can exacerbate AD, by intensifying neuroinflammation in the brain, while metabolites from anti-inflammatory bacteria in healthy digestive tract maintain cognitive functions. Bacterial amyloids can enter the systemic circulation aggravating inflammation in the brain as a consequence of the increased permeability of the intestinal barrier induced by the microbial dysbiosis at gut level (Zhao et al., 2017). Modification of the gut MB composition can be induced by high-fat diets, at least in mice, and has direct effects on gut permeability. Furthermore, a reduction of Lactobacillus, Bacteroides and Prevotella species and an increase of Bifidobacterium species, accompanied by reduced expression of both zonulin and occludin proteins (involved in epithelia permeability), have been reported in mice fed with unsaturated fatty acid diet. These features corresponded also to a higher circulatory level of the bacterial lipopolysaccharide (LPS) and other pro-inflammatory markers. Interestingly, high serum LPS, accumulation of bacterial LPS in the brain, together with monocyte activation, were reported in AD patients compared with healthy individuals. Thus, an impaired MB can modify the levels of bacterial products and amyloids in the serum, and may play a key role in AD neurodegeneration.

The correlations between the gut microbial dysbiosis and AD features are reported in **Figure 1A**.

Bacteria with a beneficial effect on the health of host recipient are probiotics, while food for these bacteria are substances called prebiotics.

Physical exercise and probiotics administration in APPPS1 transgenic mice have shown to exert beneficial effects on amyloid accumulation in the hippocampal area of mice brain (D'Argenio and Sarnataro, 2019). Furthermore, three strains of lactobacilli and Bifidobacterium bifidum, were shown to improve cognitive functions in AD patients (D'Argenio and Sarnataro, 2019). Recently, probiotics consisting of 8 strains mixture of lactic acid-producing bacteria were shown to significantly ameliorate intestinal dysfunction, and slightly Aβ plaque load, in a mouse model of AD (Kaur et al., 2020). Bifidobacterium and lactic acid bacteria have shown the ability to suppress neuroinflammation, which is a key element in amyloid accumulation and AD progression. Moreover, Bonfili et al. (2020) have assessed that oral probiotic administration in 3xTg-AD mice, through a manipulation of the gut MB, is able to decrease phosphorylated tau aggregates.

Since some bacteria in the gut are able to consume food-derived tryptophan (an amino acid with a key role in cellular aging and serotonin pathway), and can regulate tryptophan availability (D'Argenio and Sarnataro, 2019), in addition to probiotic administration, intervention with the prebiotic tryptophan has been recently reviewed. Therefore, manipulation of gut microbiota may represent a strategy for regulating tryptophan availability and reduce the production of neurotoxic derivatives, with the aim to reduce the severity of AD. In this context, Hoffman et al. (2020) showed that also the dietary supplementation with the prebiotic inulin in E4FAD mice increases short chain fatty acids production and reduces neuroinflammation.

Several neurotransmitters, like noradrenalin, serotonin, dopamine, and acetylcholine, are produced by MB, whose impairment, in turn can change neurotransmitters level in the brain and the autophagic flux. Furthermore, short-chain fatty acids, such as acetate and propionate, are able to pass the blood-brain barrier and have neuroactive properties.

Interestingly, acetate, a metabolite of the Bifidobacterium breve strain A1, ameliorates cognitive disturbance in AD mouse model and in humans (Kobayashi et al., 2017, 2019), and *in vitro* studies with photo-induced crosslinking of unmodified proteins found that butyric, valeric, propionic and isovaleric acids (metabolites from Bacillus and Bifidobacterium species) inhibit oligomerization of Aβ1–40 (Ho et al., 2018), and were found to interfere with astrocyte and microglia activation with beneficial effect on AD development by reducing

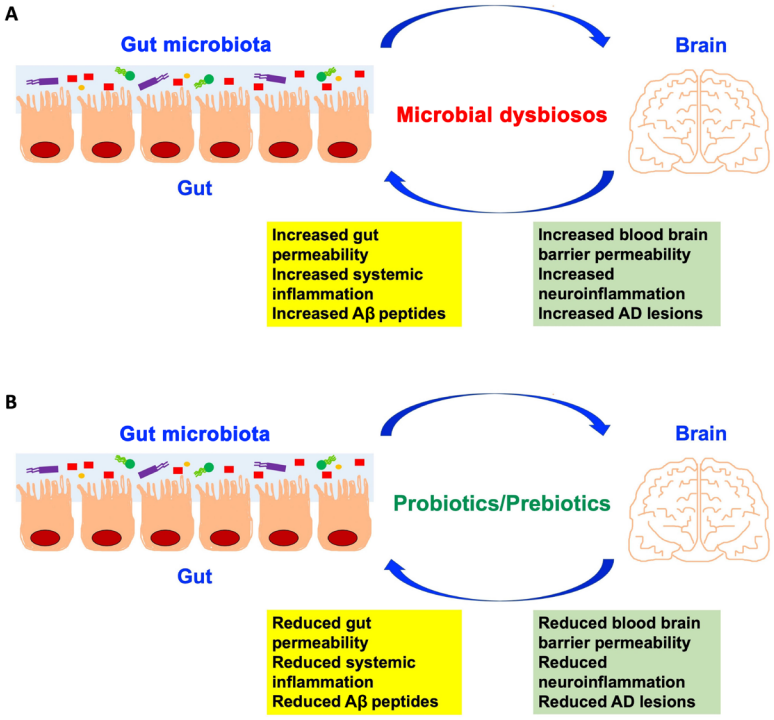

Figure 1 | **Graphical representation of the correlation between the gut microbiota and brain functions.**
A bacterial dysbiosis at gut level exerts pathogenic effects, i.e., altered gut permeability, systemic activation of the immune system, bacterial amyloid-beta (Aβ) fibrils production, increased neuroinflammation, and increased Aβ fibrils deposition at the brain level, that contribute to Alzheimer's disease (AD) development (A). The use of probiotics/prebiotics, by restoring a "healthy" gut microbiota, is able to ameliorate one or more of these aspects showing promising potentialities in AD prevention and/or treatment (B).

inflammation (Macfarlane et al., 2012).

Prebiotic effect of fructooligosaccharides from Morinda officinalis on AD has been evaluated in rodent models by targeting the microbiota-gut-brain axis. This study reported a significant improvement of cognitive functions after prebiotic treatment.

Even if most of the studies published to date have been carried out on AD mouse models, some translational studies are showing promising evidences also in humans. A randomized, double-blind, controlled clinical trial involving 79 AD patients showed that the co-supplementation of probiotic and selenium for 12 weeks determines an improvement of cognitive and metabolic functions (Tamtaji et al., 2019).

Taken together, these studies suggest that a personalized diet and/or pro/prebiotic or symbiotic (combination of bioactive probiotics) administration, by modulating the gut microbiota, may represent a new treatment for AD. The mechanisms through which the gut microbiota manipulation may ameliorate some AD specific treats are summarized in **Figure 1B**.

The use of probiotics and prebiotics in clinical practice still lacks robust evidence. However, since recent data in specific aging-related disorders are encouraging, we can seriously consider to modify the intestinal microflora with pro- and/or pre-biotics to obtain beneficial effects in the prevention and treatment of AD.

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