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Increased ileal bile acid binding protein and galectin-9 are associated with mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Enterocyte damage and subsequent microbial translocation drive neuroinflammation in the pathogenesis of Alzheimer's disease (AD). Human ileal bile acid binding protein (I-BABP) and intestinal fatty acid binding proteins (I-FABP) are the indicators of enterocyte damage. Lipopolysaccharide-binding protein (LBP) is an indirect marker of microbial translocation. The activation of peripheral innate immune cells plays a crucial role in modulating AD progression. Galectin-9 is a versatile immunomodulatory molecule. The purpose of this study was to determine I-FABP, I-BABP, LBP, and galectin-9 levels in MCI and AD and investigate the relationship between I-FABP, I-BABP, LBP and galectin-9. In this study, I-FABP, I-BABP, LBP, and galectin-9 levels were measured using ELISA assay in 115 AD patients, 115 MCI patients, and 115 non-demented control subjects. Increased I-BABP and galectin-9 were observed in MCI and AD patients. Furthermore, AD patients had higher I-BABP and galectin-9 levels compared with MCI patients. However, I-FABP and LBP in three groups had no difference. I-BABP levels were positively correlated with galectin-9, after adjusting confounding factors ($r = 0.409$, $p < 0.001$). In addition, multivariate analysis revealed that increased I-BABP and galectin-9 levels were significantly associated with reduced mini-mental state examination (MMSE) score. In conclusion, galectin-9 is correlated with I-BABP after adjusting confounding covariates. Moreover, increased I-BABP and galectin-9 in MCI and AD are significant factors for reduced MMSE score. Further studies are needed.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia among elderly, is clinically characterized by the progressive cognitive impairment. Mild cognitive impairment (MCI) is an intermediate stage from normal aging to dementia. Although much progress has been made in the treatment of AD in recent years, there are no effective drug to stop the progressive cognitive decline. Therefore, further investigation on the mechanisms of AD is of great importance.

Alterations in the gut microbiota composition induce increased permeability of the gut barrier, which in turn impairs the blood-brain barrier and promotes neuroinflammation and ultimately neurodegeneration (Kowalski & Mulak, 2019). Intestinal fatty acid binding proteins are small proteins released into the circulation upon enterocyte membrane integrity loss, which makes them sensitive markers of damage to the intestinal epithelium (Schellekens et al., 2014). Human ileal bile acid binding protein (I-BABP) only exists in the small intestine and indicates enterocyte damage. Intestinal fatty acid binding proteins (I-FABP), another marker of enterocyte damage, is present in the small or large intestine. Lipopolysaccharide-binding protein (LBP) is an indirect marker of microbial translocation.

Accumulating evidence suggest that changes in the dynamic interplay between gut microbiota, intestinal epithelial barrier and enteric neuro-immune system might represent the starting point of the neurodegenerative process (Pellegrini et al., 2018). A diverse and rich gut microbiota plays an essential role in the development and maturation of the host immune system (Zhao & Elson, 2018). Galectin-9, a member of the β-galactoside-binding lectin family, is expressed in different tissues and cells in humans. Galectin-9 is a versatile immunomodulatory molecule involved in a wide range of biological activities such as cell adhesion and migration, proliferation, apoptosis, interaction with microbial pathogens, Tregs differentiation and function, dendritic cell maturation, and antimicrobial immunity (Merani et al., 2015).

The aim of this study is to examine the associations of I-FABP, I-

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Table 1
Clinical characteristics of the participants.

	Control	MCI	AD	*p* value
N	115	115	115	
Age (years)	75.7 ± 3.8	75.6 ± 3.6	75.9 ± 4.0	0.858
(range)	(68–83)	(69–87)	(68–85)	
Gender (male, %)	40 (34.8)	37 (32.2)	41 (35.7)	0.846
BMI (kg/m^2)	22.6 ± 3.3	22.3 ± 2.2	20.7 ± 2.3	< 0.001
Education (years)	10.8 ± 2.3	10.8 ± 2.1	10.3 ± 2.2	0.174
Smoking (%)	23 (20.0)	21 (18.3)	20 (17.4)	0.874
Platelet count ($\times 10^9$/L) 216.4 ± 56.6	229.7 ± 52.7	220.8 ± 52.4	0.166	
WBC ($\times 10^9$/L)	6.1 ± 1.4	6.2 ± 1.4	6.1 ± 1.5	0.895
LBP (ug/mL)	0.112 ± 0.009	0.113 ± 0.037	0.107 ± 0.015	0.189
I-FABP (ng/mL)	0.059 ± 0.002	0.058 ± 0.003	0.059 ± 0.004	0.323
MMSE score	27.9 ± 1.5	24.8 ± 0.8	14.5 ± 2.2	< 0.001
CDR	0	0.5	1.3 (0.5)	< 0.001
Hypertension (%)	33 (28.7)	35 (30.4)	32 (27.8)	0.906
Type 2 diabetes (%)	26 (22.6)	27 (23.5)	22 (19.1)	0.699
CAD (%)	26 (22.6)	23 (20.0)	21 (18.3)	0.711

MCI, mild cognitive impairment; AD, Alzheimer's disease; BMI, body mass index; MMSE, mini-mental state examination; WBC, white blood cell; CDR, clinical dementia rating; CAD, coronary atherosclerotic heart disease. Values are shown as mean (standard deviation) or median (IQR) or percentage. *p* value was calculated by one-way ANOVA test or Kruskal-Wallis H test or chi-square test.

BABP, LBP, and galectin-9 levels with healthy controls, patients with MCI, and patients with AD.

2. Materials and methods

2.1. Participants

115 AD patients (mean age 75.7 ± 3.8 years), 115 subjects with MCI (mean age 75.6 ± 3.6 years), and 115 non-demented control subjects (mean age 75.9 ± 4.0 years) were recruited from the Second Hospital of Harbin Medical University between January 2017 and December 2017. We selected age and gender matched non-demented control subjects with similar educational levels. All the subjects underwent a clinical investigation including medical history, and physical, neurological, and psychiatric examinations, laboratory tests, and an MRI scan of the brain. Medical history, smoking status and medication use were recorded for each participant.

The study was approved by the Ethics Committee of the Second Hospital of Harbin Medical University, China. All participants provided written informed consent.

2.2. Diagnosis and exclusion criteria

Global cognitive function was assessed by the mini-mental state examination (MMSE). Inclusion criteria are as follows: (1) Normal subjects: MMSE scores between 24 and 30, clinical dementia rating (CDR) of 0, non-MCI, and nondemented. (2) MCI patients: MMSE scores between 24 and 30, memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and nondemented (Winblad et al., 2004). (3) Probable AD: an MMSE between 20 and 26, CDR total score equal to 0.5 or 1.0, fulfill the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria.

Exclusion criteria included infection, depression, Parkinson's disease, chronic alcoholism, autoimmune diseases, tumor, chronic liver and kidney diseases, and abnormal vitamin B_{12} or thyroid function tests.

Coronary atherosclerotic heart disease (CAD) was defined as the occurrence of a nonfatal myocardial infarction, a percutaneous coronary angioplasty, other forms of acute or chronic ischemic heart disease.

2.3. Blood sampling and laboratory tests

Venous blood was drawn from subjects after a 12-h over-night fast. After collection, the samples were immediately centrifuged at 3000 × g for 15 min. Sesum was subsequently removed and stored at −80 °C until ELISA assay.

I-FABP, I-BABP, LBP, and galectin-9 levels were measured by ELISA commercial assays, according to the manufacturers' instructions (*CUSABIO*, Wuhan, China). Samples were tested as duplicates. The sensitivities for I-FABP, I-BABP, LBP, and galectin-9 assays were 0.625 ng/mL, 0.078 ng/mL, 0.125 μg/mL, and 7.8 pg/mL, respectively. The intra and inter-assay coefficients of variation for I-FABP, I-BABP, LBP, and galectin-9 assays were < 8% and 10%, respectively.

2.4. Statistical analysis

Statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as means ± SD or median (IQR) or absolute number (percentage). For comparisons of data among groups, continuous variables were analyzed by one-way ANOVA, and Post hoc analyses using two-tailed LSD were done to compare the differences between the groups. Categorical data were analyzed using Chi-square test. Comparisons of proportions between the groups were tested using Rank Sum Test. Partial correlation was conducted to analyze correlations between continuous variables. Multivariate analysis was performed using linear regression model to determine the relationships between MMSE and various clinical variables. A value of $p < 0.05$ was regarded as a significant difference.

3. Results

Table 1 lists the demographic and clinical characteristics of subjects according to the different groups. There were significant differences in BMI, CDR and MMSE score among three groups ($p < 0.001$). However, age, gender, education levels, smoking status, platelet count, white blood cell, LBP, I-FABP, hypertension, type 2 diabetes, and CAD in three groups had no difference.

The I-BABP and galectin-9 levels in control group, MCI group and AD group are shown in Fig. 1 and Fig. 2. Serum I-BABP levels were significantly higher in patients with AD than those in patients with MCI or control subjects. Moreover, serum I-BABP levels were increased in MCI group compared with those in control subjects. Serum I-BABP levels in AD, MCI, and control subjects were 0.100 ± 0.004, 0.122 ± 0.017, and 0.142 ± 0.093 ng/ml, respectively (Fig. 1).

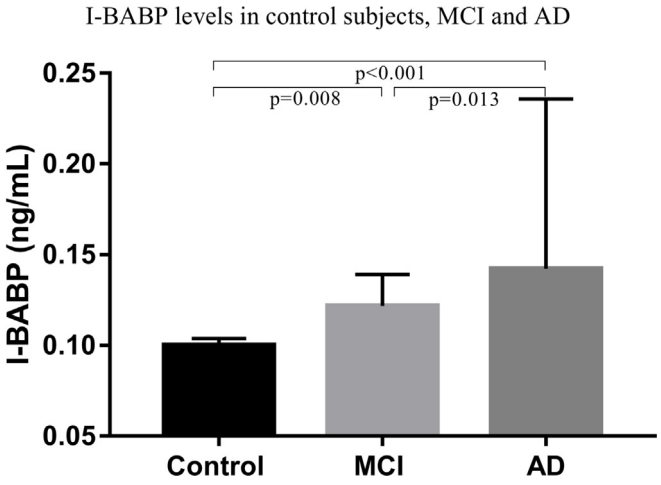

Fig. 1. I-BABP in control subjects, MCI and AD.

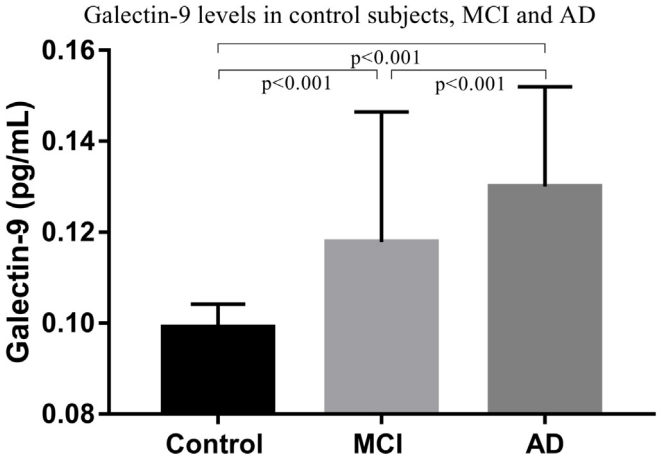

Fig. 2. Galectin-9 in control subjects, MCI and AD.

Similarly, serum galectin-9 levels were significantly higher in AD patients than those in MCI patients or control subjects. Furthermore, serum galectin-9 levels were increased in MCI group compared with those in control subjects. Serum galectin-9 levels in AD, MCI, and control group were 0.099 ± 0.005, 0.118 ± 0.029, and 0.130 ± 0.022 pg/ml, respectively (Fig. 2).

The correlations between I-BABP and galectin-9 after adjustment for other covariates are presented in Fig. 3. The correlation coefficient between I-BABP and galectin-9 was 0.441 ($p < 0.001$). After adjusting for age, gender, BMI, smoking, and education levels, the partial correlation coefficient between I-BABP and galectin-9 was 0.425 ($p < 0.001$). In addition, after adjusting for age, gender, BMI, smoking, education levels, white blood cell, platelet count, hypertension, CAD, and type 2 diabetes, the partial correlation coefficient between I-BABP and galectin-9 was 0.409 ($p < 0.001$).

The participants distribution according to I-BABP and galectin-9 quartiles in control, MCI, and AD group was shown in Table 2. The results revealed a significant difference of I-BABP levels among three groups (control group vs. MCI group, $P < 0.001$; control group vs. AD group, $p < 0.001$; MCI group vs. AD group, $p = 0.001$). Similar results were found according to galectin-9 quartiles (control group vs. MCI group, $p < 0.001$; control group vs. AD group, $p < 0.001$; MCI group vs. AD group, $p < 0.001$).

Multivariate linear regression analysis was used to assess the relationship between MMSE score and clinical variables (Table 3). BMI, I-BABP and galectin-9 were significantly associated with MMSE score in the multivariate model. Notably, increased I-BABP and galectin-9 levels

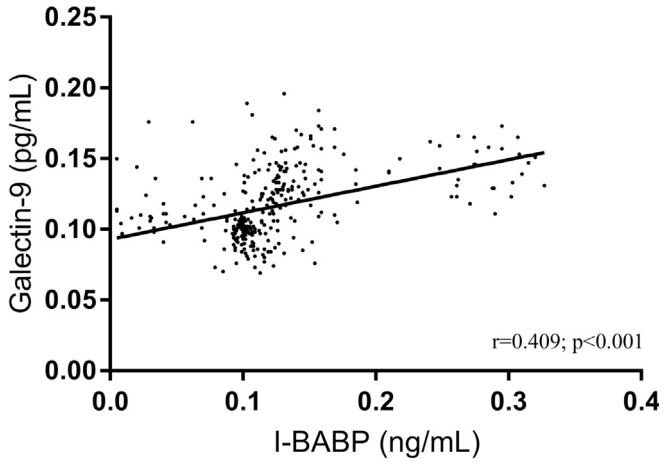

Fig. 3. Partial correlation of I-BABP with galectin-9 after adjusting for other covariates.

Table 2
The participants distributed according to I-BABP and galectin-9 quartiles.

	Q1	Q2	Q3	Q4
I-BABP (ng/mL)	≤ 0.099	0.100-0.107	0.108-0.131	≥ 0.132
Control (n)	42	70	3	0
MCI (n)*	10	10	67	28
#AD (n)*	42	5	11	57
Total (n)	94	85	81	85
Galectin-9 (pg/mL)	≤ 0.099	0.100-0.107	0.108-0.132	≥ 0.133
Control (n)	46	66	3	0
MCI (n)*	41	3	36	35
#AD (n)*	4	16	45	50
Total (n)	91	85	84	85

*$P < 0.001$ compared with the control group.
#$P < 0.001$ when MCI group compared with AD group.

Table 3
Multivariate linear regression analysis with MMSE as the dependent variable.

Variables	β	*p* value
I-BABP (ng/mL)	- 0.102	0.037
Galectin-9 (pg/mL)	- 0.380	< 0.001
BMI (kg/m^2)	0.251	< 0.001

MMSE, mini-mental state examination; BMI, body mass index. β, standardized regression coefficients. The *p* value for entry was set at 0.05, and the *p* value for removal was set at 0.10. Adjusted $R^2 = 0.274$, $p < 0.001$.

were the significant factors for decreased MMSE score (β = - 0.102; $p = 0.037$ for I-BABP; β = - 0.380; $p < 0.001$ for galectin-9).

4. Discussion

Our study observed that AD patients had higher I-BABP and galectin-9 levels than MCI patients. Moreover, I-BABP was significantly positively correlated with galectin-9. Multivariate regression analysis further revealed that increased I-BABP and galectin-9 were the significant factors for decreased MMSE score.

The role of gut microbiota in the pathophysiology of Alzheimer's disease, has recently come under intense investigation (Junges et al., 2018). The diversity of the gut microbiota declines in AD patients. Restoring the diversity with probiotic treatment alleviates the psychiatric and histopathological findings in AD (Bostancikliоğlu, 2019). Moreover, modulation of the composition of gut microbiota may decrease the risk of AD and be able to slow down the progression of AD (Szablewski, 2018). Further research demonstrated that microbes in the gut profoundly affect the development of microglia and effectively

prime microglia in the brain via secreted short-chain fatty acids (Erny et al., 2015; Thion et al., 2018).

The interactions between the brain and the periphery have a crucial role in the development and progression of AD (Wang et al., 2017a,b). The central and peripheral pathways of Aβ metabolism communicate with each other, and work synergistically to clear Aβ from the brain (Wang et al., 2017a,b). A previous report found that impaired hepatic Aβ degradation could be a factor contributing to increased brain Aβ accumulation and AD (Maarouf et al., 2018). A recent study confirmed that hepatic dysfunction could lead to reduced Aβ excretion in bile and impaired Aβ clearance in hepatocytes (Wang et al., 2017a,b).

Emerging evidence showed that oxidized cholesterol metabolites known as oxysterols are able to cross the blood brain barrier and influence the progression of AD (Loera-Valencia et al., 2019). Cholesterol is synthesized in liver and its clearance involves bile acid production by gut microbiome and human co-metabolism. Gut microbiota are vital to the transformation of bile acid. Recent studies revealed that bile acids are altered MCI and AD (Nho et al., 2019). In addition, increased levels of secondary bile acids were strongly associated with cognitive decline in AD (MahmoudianDehkordi et al., 2019). Disturbed bile acids were confirmed in brain extracts and blood plasma from AD patients (Pan et al., 2017). Moreover, previous studies demonstrated that tauroursodeoxycholic acid is an endogenous anti-apoptotic bile acid with potent neuroprotective properties in AD (Dionísio et al., 2015; Lo et al., 2013; Ramalho et al., 2013). I-BABP, a key component of bile acid recycling system, regulates bile acid activity in the small intestine (Nakahara et al., 2005). When exposed to bacteria or gluten, the small intestine can increase intestinal permeability and disrupt intestinal barrier function, leading to abnormal antigen presentation to the intestinal submucosa, and triggering inflammation and adaptive immune response (El et al., 2002; Fasano, 2011). In addition, a report revealed that the bile acid modulated intestinal innate immunity via farnesoid X receptor (Vavassori et al., 2009). We observed a significant increase in I-BABP levels in MCI and AD, suggesting that the change of bile acids in small intestine is a contributing factor to the cognitive deterioration.

Recent research demonstrated that galectin-9 is a pleiotropic immune modulator affecting both innate and adaptive immune responses. Galectin-9 exerts its pivotal immunomodulatory effects by inducing apoptosis or suppressing effector functions via engagement with its receptor, T cell immunoglobulin mucin domain 3. There is plenty of evidence of T cell infiltration into the brain in AD patients (McManus et al., 2015). Moreover, previous reports showed proinflammatory $CD4^+$ T cells exacerbate neuroinflammation while regulatory and anti-inflammatory $CD4^+$ T cells are neuroprotective in AD (Dansokho et al., 2016; Sommer et al., 2017). Many autoimmune diseases arise from an imbalance between pathogenic effector T cells and regulatory T (Treg) cells. Recent studies found that the cross-talk between gut microbiota and the host immune system promotes autoimmune development by controlling the differentiation and plasticity of T helper and Treg cells (Sprouse et al., 2019). Our study indicated that I-BABP maybe act synergistically with T cells to accelerate the progression of cognitive deterioration. Further research on the association between I-BABP and galectin-9 is warranted.

Some limitations of our study need to be addressed. Firstly, the sample size is small. Secondly, it is a case-control study and we were not able to infer causality. The findings need to be confirmed in further longitudinal studies. Thirdly, the diagnosis of probable AD needed to be confirmed, since no plaque imaging or Abeta levels were analyzed to be positive for AD diagnosis. Finally, it should be cautious to apply the results to other ethnic groups because the patients were composed of Chinese.

In conclusion, higher I-BABP and galectin-9 levels were found in MCI and AD patients. Moreover, I-BABP levels were significantly positively correlated with galectin-9 levels. Additionally, increased I-BABP and galectin-9 were the significant factors for decreased MMSE score. Further study is needed.

Authors' contributions

RT W conceived the study; X W, Y N, and RT W participated in the design; X W, Y N, CX Y and S F collected the data; and X W and Y N performed statistical analyses. X W and Y N drafted the manuscript. CX Y, RT W, and S F edited and checked the manuscript. All of the authors have read and approved the final manuscript.

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Declaration of competing interest

None.

References

Bostancikliоğlu, M., 2019. The role of gut microbiota in pathogenesis of Alzheimer's disease. J. Appl. Microbiol.
Dansokho, C., Ait, A.D., Aid, S., et al., 2016. Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain 139, 1237–1251.
Dionísio, P.A., Amaral, J.D., Ribeiro, M.F., et al., 2015. Amyloid-β pathology is attenuated by tauroursodeoxycholic acid treatment in APP/PS1 mice after disease onset. Neurobiol. Aging 36, 228–240.
El, A.R., Panigrahi, P., Bamford, P., et al., 2002. Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure. Gastroenterology 123, 1607–1615.
Erny, D., de Angelis AL, H., Jaitin, D., et al., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18, 965–977.
Fasano, A., 2011. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol. Rev. 91, 151–175.
Junges, V.M., Closs, V.E., Nogueira, G.M., et al., 2018. Crosstalk between gut microbiota and central nervous system: a focus on Alzheimer's disease. Curr. Alzheimer Res. 15, 1179–1190.
Kowalski, K., Mulak, A., 2019. Brain-gut-microbiota Axis in Alzheimer's disease. J. Neuro Gastroenterol. Motil. 25, 48–60.
Lo, A.C., Callaerts-Vegh, Z., Nunes, A.F., et al., 2013. Tauroursodeoxycholic acid (TUDCA) supplementation prevents cognitive impairment and amyloid deposition in APP/PS1 mice. Neurobiol. Dis. 50, 21–29.
Loera-Valencia, R., Goikolea, J., Parrado-Fernandez, C., Merino-Serrais, P., Maioli, S., 2019. Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: potential novel targets for treatment. J. Steroid Biochem. Mol. Biol. 190, 104–114.
Maarouf, C.L., Walker, J.E., Sue, L.I., Dugger, B.N., Beach, T.G., Serrano, G.E., 2018. Impaired hepatic amyloid-beta degradation in Alzheimer's disease. PLoS One 13, e0203659.
MahmoudianDehkordi, S., Arnold, M., Nho, K., Ahmad, S., Jia, W., Xie, G., et al., 2019. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. Alzheimers Dement 15, 76–92.
McManus, R.M., Mills, K.H., Lynch, M.A., 2015. T cells-protective or pathogenic in Alzheimer's disease. J. Neuroimmune Pharmacol. 10, 547–560.
Merani, S., Chen, W., Elahi, S., 2015. The bitter side of sweet: the role of Galectin-9 in immunopathogenesis of viral infections. Rev. Med. Virol. 25, 175–186.
Nakahara, M., Furuya, N., Takagaki, K., Sugaya, T., Hirota, K., Fukamizu, A., et al., 2005. Ileal bile acid-binding protein, functionally associated with the farnesoid X receptor or the ileal bile acid transporter, regulates bile acid activity in the small intestine. J. Biol. Chem. 280, 42283–42289.
Nho, K., Kueider-Paisley, A., MahmoudianDehkordi, S., Arnold, M., Risacher, S.L., Louie, G., et al., 2019. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: relationship to neuroimaging and CSF biomarkers. Alzheimers Dement 15, 232–244.
Pan, X., Elliott, C.T., McGuinness, B., Passmore, P., Kehoe, P.G., Hölscher, C., et al., 2017. Metabolomic profiling of bile acids in clinical and experimental samples of Alzheimer's disease. Metabolites 7.
Pellegrini, C., Antonioli, L., Colucci, R., Blandizzi, C., Fornai, M., 2018. Interplay among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system: a common path to neurodegenerative diseases. Acta Neuropathol. 136, 345–361.
Ramalho, R.M., Nunes, A.F., Dias, R.B., et al., 2013. Tauroursodeoxycholic acid suppresses amyloid β-induced synaptic toxicity in vitro and in APP/PS1 mice. Neurobiol. Aging 34, 551–561.
Schellekens, D.H., Grootjans, J., Dello, S.A., et al., 2014. Plasma intestinal fatty acid-binding protein levels correlate with morphologic epithelial intestinal damage in a human translational ischemia-reperfusion model. J. Clin. Gastroenterol. 48, 253–260.
Sommer, A., Winner, B., Prots, I., 2017. The Trojan horse - neuroinflammatory impact of

T cells in neurodegenerative diseases. Mol. Neurodegener. 12, 78.
Sprouse, M.L., Bates, N.A., Felix, K.M., et al., 2019. Impact of gut microbiota on gut-distal autoimmunity: a focus on T cells. Immunology 156, 305–318.
Szablewski, L., 2018. Human gut microbiota in health and Alzheimer's disease. J. Alzheimer's Dis. 62, 549–560.
Thion, M.S., Low, D., Silvin, A., et al., 2018. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell 172, 500–516 e16.
Vavassori, P., Mencarelli, A., Renga, B., Distrutti, E., Fiorucci, S., 2009. The bile acid receptor FXR is a modulator of intestinal innate immunity. J. Immunol. 183, 6251–6261.
Wang, J., Gu, B.J., Masters, C.L., Wang, Y.J., 2017a. A systemic view of Alzheimer disease - insights from amyloid-β metabolism beyond the brain. Nat. Rev. Neurol. 13, 703.
Wang, Y.R., Wang, Q.H., Zhang, T., Liu, Y.H., Yao, X.Q., Zeng, F., et al., 2017b. Associations between hepatic functions and plasma amyloid-beta levels-implications for the capacity of liver in peripheral amyloid-beta clearance. Mol. Neurobiol. 54, 2338–2344.
Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van, D.C., Visser, P., Petersen, R.C., 2004. Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J. Intern. Med. 256, 240–246.
Zhao, Q., Elson, C.O., 2018. Adaptive immune education by gut microbiota antigens. Immunology 154, 28–37.