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REVIEW PAPER

Gut Microbiota Disorder, Gut Epithelial and Blood–Brain Barrier Dysfunctions in Etiopathogenesis of Dementia: Molecular Mechanisms and Signaling Pathways

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Abstract

Emerging evidences indicate a critical role of the gut microbiota in etiopathogenesis of dementia, a debilitating multifactorial disorder characterized by progressive deterioration of cognition and behavior that interferes with the social and professional functions of the sufferer. Available data suggest that gut microbiota disorder that triggers development of dementia is characterized by substantial reduction in specific species belonging to the *Firmicutes* and *Bacteroidetes* phyla and presence of pathogenic species, predominantly, pro-inflammatory bacteria of the *Proteobacteria* phylum. These changes in gut microbiota microecology promote the production of toxic metabolites and pro-inflammatory cytokines, and reduction in beneficial substances such as short chain fatty acids and other anti-inflammatory factors, thereby, enhancing destruction of the gut epithelial barrier with concomitant activation of local and distant immune cells as well as dysregulation of enteric neurons and glia. This subsequently leads to blood–brain barrier dysfunctions that trigger neuroinflammatory reactions and predisposes to apoptotic neuronal and glial cell death, particularly in the hippocampus and cerebral cortex, which underlie the development of dementia. However, the molecular switches that control these processes in the histo-hematic barriers of the gut and brain are not exactly known. This review integrates very recent data on the molecular mechanisms that link gut microbiota disorder to gut epithelial and blood–brain barrier dysfunctions, underlying the development of dementia. The signaling pathways that link gut microbiota disorder with impairment in cognition and behavior are also discussed. The review also highlights potential therapeutic options for dementia.

Keywords Dementia · Gut microbiota · Gut–brain axis · Microbiota–brain axis · Gut–microbiota–brain axis

Introduction

The gut microbiota refers to all the species of commensal microbial population that inhabits the entire gastrointestinal (GI) tract, comprising approximately 100 trillion microbes from approximately 1000 species. The gut microbiota represents over 90% of the total microbes that colonize the human body. These commensals are mainly composed of anaerobic bacteria and archaea with a fewer number of protozoa, fungi, and other microbes, inhabiting every region of the GI tract-from the mouth to the anus (Chiappelli 2018; Welcome 2018).

The gut commensal microbes of any region of the GI tract can substantially influence the health state and development or progression of diseases (Welcome 2018). These microorganisms control homeostasis and metabolism, in part through their beneficial activities on intestinal barrier and permeability (with distant effect on other histo-hematic barriers), immune system functions, GI motility, absorption of nutrients, synthesis of beneficial bioactive molecules (Alkasir et al. 2017). Though the gut microbiota has a huge beneficial role to play, it can become potentially harmful, especially under unfavorable conditions of the gut microenvironment, resulting from unhealthy nutrition, pathogenic invasion or antibiotic administration (Hu et al. 2016; Jiang et al. 2017). The harmful effects of the gut microbiota are the results of abnormal behavior of the gut microbiota,

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characterized by the presence of pathogenic microbes or substantial reduction in the proportion of the gut commensals (Welcome 2018).

Emerging studies have implicated the role of abnormal gut microbiota in the development of dementia, a devastating, multifactorial clinical syndrome, characterized by progressive deterioration of memory, attention, thinking, comprehension, language, and behavior (personality), severe enough to interfere with occupational or social functions, which leads to disability, and subsequently death of the individual (Araos et al. 2018; Bäuerl et al. 2018; Buford 2017; Santocchi et al. 2016; Chertkow et al. 2013; de Jager et al. 2017; James and Schneider 2010). The growing prevalence of dementia poses a serious public health concern worldwide (Fratiglioni et al. 1999; Hung et al. 2016; Rizzi et al. 2014; Wimo et al. 2006). Dementia is associated with high financial burden to the caregiver, family, and healthcare system (Wimo et al. 2006; Hung et al. 2016; Neugroschl and Wang 2011; Wimo et al. 2010). The constantly growing prevalence and burden of the disease indicate the necessity to investigate the complex mechanisms that underlie the development of dementia and search for newer options that could provide potential therapeutic portions for the disease.

Available data suggest that gut microbiota disorder, which triggers development of dementia, is characterized by substantial reduction of specific species belonging to the *Firmicutes* and *Bacteroidetes* phyla as well as presence of pathogenic species, mainly pro-inflammatory bacteria of the *Proteobacteria* phylum. The dysbalance in the composition of gut microbiota microecology promotes the production of toxic metabolites and pro-inflammatory cytokines, and reduces the quantity of beneficial substances such as short chain fatty acids (SCFAs) and other anti-inflammatory factors, thereby, enhancing destruction of the gut epithelial barrier with activation of local and distant immune cells as well as dysregulation of enteric neurons and glia. This leads to blood–brain barrier dysfunctions that trigger neuroinflammation, predisposing to apoptotic neuronal and glial cell death, particularly in the hippocampus and cerebral cortex, which underlie the development of dementia. Interestingly, recent clinical trials with fecal microbiota transplantation (Zhao et al. 2017) or probiotics (Akbari et al. 2016; Akkasheh et al. 2016; Jamilian et al. 2016; Santocchi et al. 2016) have shown that beneficial microbes can be used to treat behavioral and cognitive impairment. Furthermore, accumulating evidences indicate an integral role of the gut microbiota in host metabolic regulation, inflammation, synthesis of a range of substances that mediate neurohumoral responses, and age-related changes associated with the gut microbiota and gut itself (Alkasir et al. 2017; Fransen et al. 2017; O'Toole and Jeffery 2015). However, the molecular switches that control these processes in the histo-hematic barriers of the gut and brain are not exactly known.

This review integrates very recent data on the molecular mechanisms that link gut microbiota disorder to gut epithelial and blood–brain barrier dysfunctions, underlying the development of dementia. The signaling pathways that link gut microbiota disorder with impairment in cognition and behavior are also discussed. The review also highlights potential therapeutic options for dementia.

Overview of Etiopathogenesis of Dementia

Dementia is usually caused by neurological diseases (Chaudhuri et al. 2011; Du et al. 2018; Inglese and Petracca 2013; Robinson et al. 2015). Though Alzheimer's disease accounts for approximately 60–75% of all cases of dementia worldwide (Alkasir et al. 2017; Dong et al. 2012; Hung et al. 2016), the condition can also occur in up to 80% of Parkinson's disease patients (Fiest et al. 2016). Known causes of dementia are presented in Table 1.

The brain disorders (Table 1) lead to inflammation or dysfunctions in neural or glial metabolism that eventually results in loss of connections, and eventually death of brain cells (Alkasir et al. 2017; Rizzi et al. 2014). However, depending on the physiological reserve of the organism and induction of the compensatory mechanisms, cognitive impairment leading to dementia may be static, progressive, or reversible (Chaudhuri et al. 2011).

Several studies have shown that protein glycosylation due to senescence form advanced glycation endproducts can induce protein cross-linking, resulting to induction of oxidative stress and free radical formation, and possibly formation and accumulation of beta-amyloid, initiating inflammatory reactions as in the case of Alzheimer's progressive cognitive impairment or dementia (Cai et al. 2014a, b; Ray et al. 2016; Takeuchi and Yamagishi 2008; Thome et al. 1996; Tóbon-Velasco et al. 2014). The receptors for the toxigenic metabolites and pro-inflammatory molecules in neurons and glia (microglia and astrocytes) are believed to mediate the pathological processes observed in dementia (Table 2).

The receptors (Table 2) are generally termed pattern recognition receptors (PRRs) (Gordon 2002; Kalantari 2018; Takeuchi and Akira 2010). This is because they sense and recognize certain motifs on pathogens (pathogen-associated molecular patterns, PAMPs) or molecules released due to cellular damage (damage-associated molecular patterns, DAMPs) (Table 3).

PAMPs trigger the production of pro-inflammatory cytokines that may initiate the onset of certain peripheral and central diseases characterized by inflammatory reactions (Welcome 2018).

The recognition of PAMPs or DAMPs by PRRs (e.g., TLRs, CD14) activates signaling pathways such as nuclear factor kappa of B cell (NF-κB) and inducible nitric oxide synthase (iNOS) leading to the synthesis of

Table 1 Causes of dementia

Disease category	Types	References
Neurological disease	Alzheimer's disease, multiple sclerosis, and Parkinson's disease	Alkasir et al. (2017), Chaudhuri et al. (2011), Du et al. (2018), Inglese and Petracca (2013), Robinson et al. (2015), Sambamurti et al. (2002)
Cerebrovascular disease	Ischemic and hemorrhagic stroke	Corraini et al. (2017), Shi et al. (2017), Knopman (2006), Tang et al. (2017)
Infections	Creutzfeldt-Jakob disease, herpes simplex virus type 1, human immunodeficiency virus, syphilis, borrelia, toxoplasmosis, cryptococcus, cysticercosis, cytomegalovirus, *Helicobacter pylori*, *Chlamydophila pneumoniae*, *Borrelia burgdorferi*,	Licastro and Porcellini (2016), Katan et al. (2013), Sochocka et al. (2017), Almeida and Lautenschlager (2005), Mawanda and Wallace (2013), Rizzi et al. (2014)
Inherited disorders	Huntington's chorea, Niemann-Pick disease type C	Roos (2010), Cupidi et al. (2017)
Drugs	Alcohol, benzodiazepines, antihypertensives, anticholinergics, tobacco, cannabis	Starr and Whalley (1994), Hulse et al. (2005), Johnell (2015), Ridley et al. (2013), Richardson et al. (2018)
Others	Normal pressure hydrocephalus, prion diseases, progressive supranuclear palsy, corticobasal syndrome	Wenning et al. (1998), Zamboni et al. (2010), Kobylecki et al. (2015), Martin (2006), Shprecher et al. (2008), Di Fede et al. (2018), Geschwind (2010)

pro-inflammatory cytokines (Fig. 1) (Friedland and Chapman 2017; Kim et al. 2011; Land 2015; Li et al. 2015; McCarthy et al. 2014; Rangaraju et al. 2018). This pathway of pro-inflammatory cytokine synthesis is termed MyD88-dependent as it is mediated via the cytoplasmic adaptor protein myeloid differentiation primary-response protein 88 (MyD88) (Fig. 1). However, there is also MyD88-independent pathway that controls IFNβ synthesis and activity (Welcome 2018). This "recognition signaling" occurs at the local (gut epithelium) and central levels (brain) (Fig. 1).

It should be mentioned, however, that there are multiple pathways through which the cell recognizes pathogenic microbes. The pattern recognition molecules MBL (mannose-binding lectin) and ficolins functioning as opsonins link up with MBL-associated serine protease-2 (MASP-2), forming MBL-MASP-2 complex, which recognizes and subsequently binds to carbohydrate molecules of bacterial cell wall to initiate series of reactions that culminate in production of pro-inflammatory cytokines, which in turn leads to altered balance or composition of resident microbes of the gut (Hartz et al. 2017; Li et al. 2016; Asgari et al. 2014; Bjarnadottir et al. 2016), and increased intestinal permeability (Fig. 2) (Degn et al. 2013; Kilpatrick and Chalmers 2012; Møller-Kristensen et al. 2007; Welcome 2018).

The pro-inflammatory cytokines can be transported to different tissues including the brain, initiating neuroinflammatory process in the blood–brain barrier that decreases its permeability (Bonfili et al. 2017; Foster et al. 2017). It should be mentioned, however, the molecular switches or fingerprints that drive activation of MBL-MASP-2 complex, initiating intestinal epithelial injury have not been clearly defined. Sandahl et al. (2014) reported that MBL or ficolin activation of MASP-2 that subsequently formed the MBL(or ficolin)-MASP-2 complex was the main process that trigger gut epithelial injury. Thus, it can be speculated that some sought of immune tuning may be essential as a switch from normal gut functioning to abnormal gut epithelial barrier dysfunctions. Moreover, Megyeri et al. (2013) and Héja et al. (2012) reported that MASP-2 is capable of auto-activation. The intrinsic mechanisms of MASP-2 activation require further investigation.

Lipocalin-2 (also known as siderocalin), a 25-kDa protein, discovered by Kjeldsen et al. (1993) from human neutrophil, is believed to be ubiquitously expressed in many tissues including the gut and brain (Nielsen et al. 1996; Thorsvik et al. 2018; Naudé et al. 2012). The purported role of lipocalin-2 in the brain has sparked considerable interest on the behavior and signaling pathways mediated by this secreted glycoprotein. Though information about the peptide remains scanty, functional lipocalin-2 forms complex with brain type organic cation transporter 1, and megalin (also known as low density lipoprotein-related protein 2) and contributes to the transport of small hydrophobic molecules

Table 2 Receptors for the toxigenic metabolites and pro-inflammatory molecules in neurons and glia (microglia and astrocytes)

Receptor types	Receptor subtypes	References
Nucleotide-binding oligomerization domain-like receptor containing pyrin domain (NLRP)	NLRP1–5, NLRP9, NLRP10	Saresella et al. (2016), Kaushal et al. (2015), Jo et al. (2016)
Triggering receptor expressed on myeloid cells (TREM)	TREM2	Woollacott et al. (2018), Rayaprolu et al. (2013)
Scavenger receptor (SR)	SR-A, SR-A6 (MARCO); SRB-1	Hickman et al. (2008), El Khoury et al. (1998), Coraci et al. (2002), Thelen et al. (2010)
Receptor for advanced-glycosylation endproducts (RAGE)	AGE—glycotoxins, methylglyoxal, carboxymethyl-lysine	Cai et al. (2014a, b), Uribarri et al. (2007), Srikanth et al. (2011)
Receptors of complement system	Fc receptors, FPR2	Doens and Fernández 2014), Crehan et al. (2012), Lian et al. (2016), Xiong et al. (2018)
Cluster of differentiation (CD)	CD11, CD33, CD36, CD45	Hu et al. (2014), Walker and Lue (2015)
Toll-like receptor type (TLR)	TLR2, TLR3, TLR4, TLR6, TLR7	Liu et al. (2012), Jana et al. (2008), Hanamsagar et al. (2012)
Chemokine receptors	CMKLR1, CXCR5	Peng et al. (2015), Stuart et al. (2014)
Prostaglandin receptors	EP2, EP4	Liang et al. (2005), Fattahi and Mirshafiey (2014), Fiebich et al. (2001)

AGE advanced-glycosylation endproducts; *FPR2* formyl peptide receptor 2; *CMKLR1*chemokine-like receptor 1, *CXCR5* C-X-C motif chemokine receptor 5; *MARCO* macrophage receptor with collagenous structure

Table 3 Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)

Ligands for PRRs	Examples	References
PAMPs	Lipopolysaccharides, peptidoglycan, lipoteichoic acid, teichoic acid, lipoarabinomannan, arabinogalactan, lipopeptides, flagellin, bacterial DNA, viral RNA	Venegas and Heneka (2017), Wozniak et al. (2009), Tanaka and Nagashima (2018), Wozniak et al. (2009), Tanaka and Nagashima (2018), Schaefer et al. (2018), Mahla et al. (2013), Mattsson et al. (2008)
DAMPs	Laminin, elastin and collagen-derived peptides, fibronectin, matrix metalloproteinases-3 and -13, versican, biglycan, heat shock proteins, RNA, mitochondrial DNA, nuclear DNA, IL-1, amyloid β, high mobility group box 1 protein, histones, adenosine triphosphate, antimicrobial peptides, S100 family proteins, chromogranin A	Kim et al. (2011), Land (2015), Skandalis et al. (2015), Theocharis et al. (2016), Welcome (2018), Venegas and Heneka (2017)

(Chia et al. 2015; Song and Kim 2018). Lipocalin-2 is implicated in inflammatory response in the gut (Thorsvik et al. 2018). Thorsvik et al. (2018) revealed high expression of lipocalin-2 in enteroendocrine cells of ileum and colon in patients with intestinal inflammation, compared to healthy control. Interestingly the microglial, astroglial, epithelial, and neuronal type of the lipocalin-2/megalin complex has been shown to be involved in neuroinflammation (Chia et al. 2015; Song and Kim 2018). It is not exactly clear how lipocalin-2 or lipocalin-2/megalin complex is formed, but previous data have shown that microbial components (e.g., LPS) can trigger the formation of lipocalin-2 (Lee et al. 2011). Furthermore, Naudé et al. (2012) showed that TNF receptor type 1 activation by TNF-α can result to the production of lipocalin-2 in murine microglia, astrocytes, and neurons (Naudé et al. 2012). Indeed lipocalin-2 production can be initiated not only by TNF, but also, IL-1β, IL17, and IL22 (Nielsen et al. 1996; Thorsvik et al. 2018). Lee et al. (2011) showed that lipocalin-2 enhances expression of chemokines in brain of mouse (Lee et al. 2011). Although the mechanisms of lipocalin-2 signaling are yet to be fully understood, available data indicate that following action of LPS or pro-inflammatory cytokines, the formation of lipocalin-2 can induce the production of chemokines (e.g., CXCL10) in brain cells via JAK2/STAT3/NF-κB pathway (Lee et al. 2011). Through this pathway, lipocalin-2 increases the level of reactive oxygen and nitrogen species as well as pro-inflammatory cytokines that subsequently leads to cell death (Lee et al. 2012). Indeed Lee et al. (2012) showed that overexpression of lipocalin-2 in glia enhanced neuronal apoptosis in glia and neuron cocultures (Lee et al. 2012). Similar results have been reported in humans where lipocalin-2 was decreased in the cerebrospinal fluid of patients with mild to progressive cognitive decline (Naudé et al. 2012). Surprisingly, the glycoprotein was however substantially elevated in postmortem brain tissues (Naudé et al. 2012)".

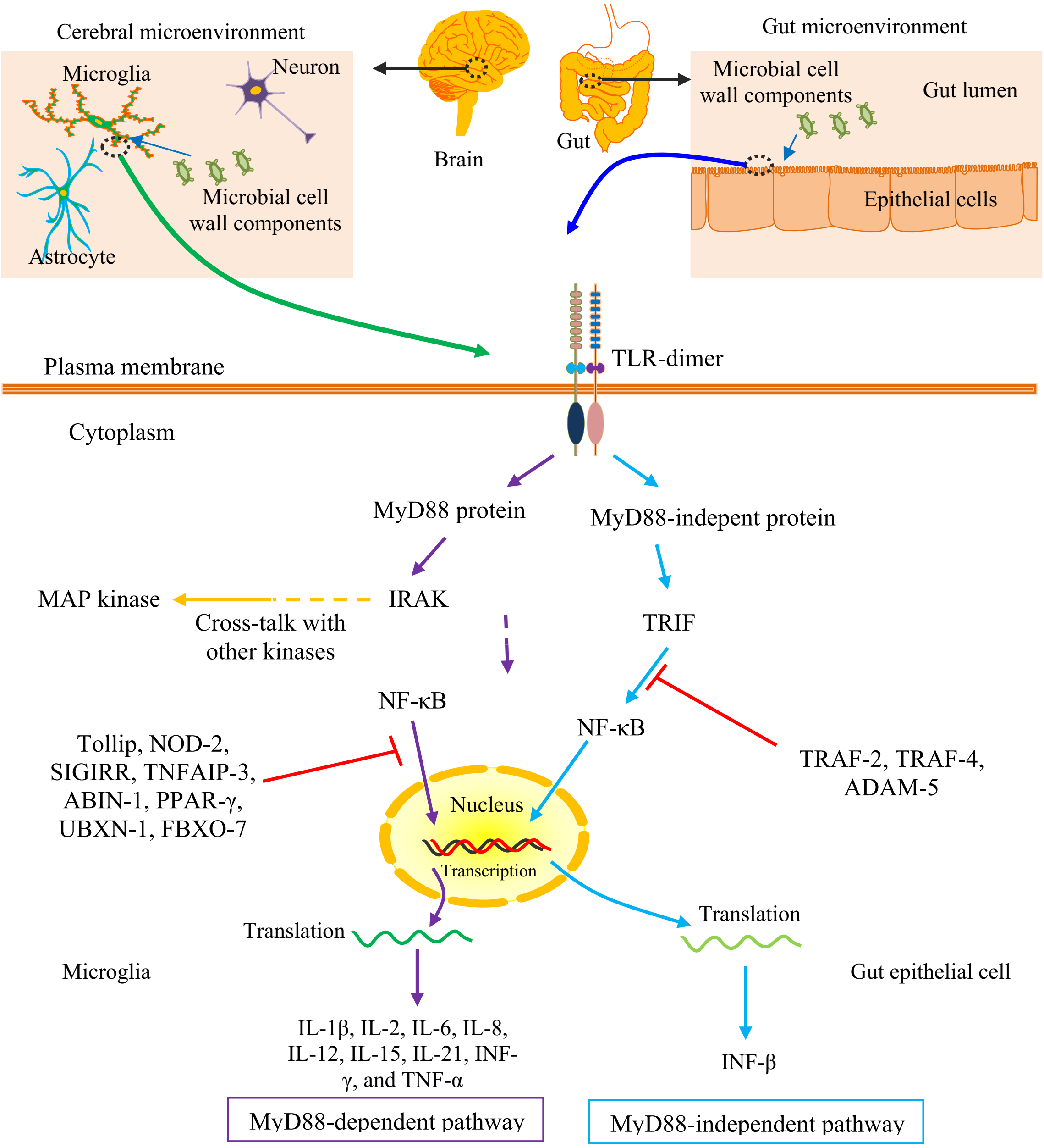

Fig. 1 A simplified schema of TLR signaling in brain cells (e.g., microglia) and cells of gut wall (enterocytes, enteroendocrine cells, enteric neurons, and glia). TLR signaling mediate downstream effect via the cytoplasmic adaptor protein myeloid differentiation primary-response protein 88 (MyD88) or intracellular proteins that are unrelated to MyD88, known as the MyD88-dependent pathway. The MyD88-dependent pathway, via activation of TLR-1, TLR-2, and TLR-6, controls the synthesis of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, IL-12, IL-15, IL-21, INF-γ, and TNF-α. TLR signaling in this pathway is negatively regulated by molecules such as toll-interacting protein (Tollip), nucleotide-binding and oligomerization domain-like receptor (NOD-2), single Ig IL-1-related receptor (SIGIRR or toll-interleukin-1 receptor), A20 (also known as TNF alpha induced protein 3, TNFAIP3, zinc finger protein), A20-binding inhibitor of NF-κB (ABIN-1, -2, -3), soluble CD83, peroxisome proliferator activated receptor gamma (PPAR-γ), ubiquitin-associated domain-containing ubiquitin regulatory X (UBX) protein (UBXN-1), and f-box protein only 7 (FBXO7) (Alkasir et al. 2017; Welcome 2018). The MyD88-independent pathway occurs through the activation of TLR3 and TLR4 and it is mediated via the TIR-domain-containing adapter-inducing interferon-β (TRIF) (Toll/IL-1 receptor inducing interferon). This pathway controls the IFN-β activity, as well as differentiation of dendritic and neuroglial (e.g., microglia) cells. The negative regulators of this pathway include TRAF-2 (TNF receptor-associated factor), TRAF-4, and ADAM-5 (a disintegrin and metalloproteinase-5). Adaptor proteins such as TIRAP and TRIF-related adaptor molecule (TRAM) are also involved in TLR signaling (Alkasir et al. 2017; Welcome 2018)

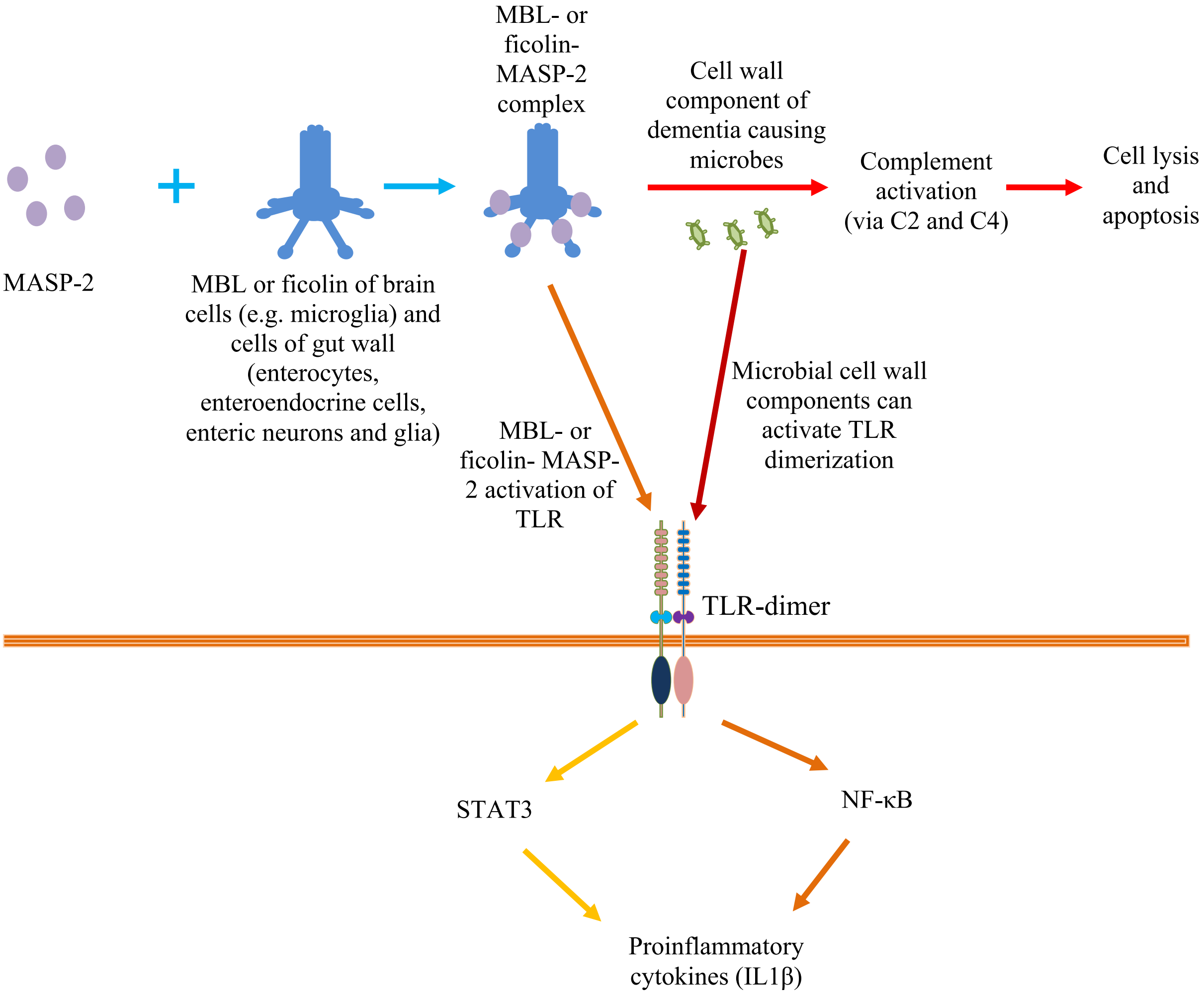

Fig. 2 MBL or ficolin–MASP-2 complex signaling. The formation of this complex triggers cellular signaling in two main pathways: inflammatory and apoptotic. The inflammatory pathway is activated via TLR, which mediates the production of pro-inflammatory cytokines through JAK-STAT (Janus kinase/signal transducers and activators of transcription) or NF-κB (nuclear factor kappa of B cells) pathway. The MBL(ficolin)–MASP-2 complex can also activate pathways of apoptotic cell death (Welcome 2018; Brady et al. 2014)

Inorganic deposits in the brain can initiate free radical processes that result in lipid peroxidation, protein oxidation, formation of reactive oxygen species, and subsequently accumulation of calcium ion that results to excitatory toxicity (Varadarajan et al. 2000). These processes underlie oxidative stress, which activates microglia, at least in part by stimulating PRRs (e.g., TLRs), resulting to phagocytosis of the toxic molecules, which may in turn lead to neurodegeneration (Chio et al. 2013; Evans et al. 1991, 1992; Gambuzza et al. 2014; Ghosh et al. 2013; Hickman et al. 2008; Millington et al. 2014; Yin et al. 2017). Previous research revealed that murine microglial cells exposed in vitro to aluminosilicate particles stimulated the generation of free radical reactive oxygen metabolites such as hydrogen peroxide, superoxide, and hydroxyl free radicals, leading to tissue injury (Evans 1992, 1993). Toxic metals activate signaling pathways related to redox transcription factors (Table 4). Indeed some deposits that characterize senile dementia have been observed to contain inorganic aluminosilicate particles in the brain of patients with progressive cognitive impairment (Evans et al. 1992). Interestingly amyloid deposits that characterize Alzheimer's disease dementia or progressive cognitive impairment in patients were shown to result in lipid peroxidation, protein phosphorylation, altering glucose metabolism, mTOR signaling pathway, leading to neuronal death (Butterfield and Boyd-Kimball 2018). Toxigenic metabolites can also cause neuroinflammmation, brain tissue or vascular injury that subsequently leads to neurodegeneration (Evans 1993; Gambuzza et al. 2014; Iemolo et al. 2009; Schneider 2007; Tong and Hamel 1999; Yin et al. 2017). Indeed dementia due to vascular dysfunction accounts for about 15–30% of all dementia cases (Chaudhuri et al. 2011).

Sanguinetti et al. (2018) recently showed an association between metabolic alterations and the composition of gut

Table 4 Redox transcription factors involved in metal induced cognitive deterioration and dementia

Transcription factors	Known metal activator	References
NF-κB	Manganese (Mn), Mn-containing dithiocarbamates, aluminum, arsenic, mercury	Williams et al. (2013), Percy et al. (2011), Di Lorenzo and Di Lorenzo (2013), Chin-Chan et al. (2015)
AP-1 (activator protein 1)	Lead, Zinc, Cadmium, Copper, Iron	Mishra and Palanivelu (2008), Myhre et al. (2013), Nitti et al. (2018)
MTF-1 (metal-responsive transcription factor 1)	Zinc, Copper, Iron	Juárez-Rebollar et al. (2017), Dong et al. (2008), Li et al. (2017)
p53 (53-kilodalton tumor protein)	Zinc, Lead, Arsenic, Mercury	Chin-Chan et al. (2015), Hwang et al. (2017), Stanga et al. (2010), Park et al. (2013), Genuis and Kelln (2015)
Ethylene responsive transcription factor 1 (ERF1), ERF2	Cadmium, Copper	Hasan et al. (2016), Koedrith and Seo (2011), Nzengue et al. (2011), Valko et al. (2005)
Ref-1 (redox factor 1)	Mercury, Cadmium	Hasan et al. (2016), Koedrith and Seo (2011), Nzengue et al. (2011), Valko et al. (2005), Genuis and Kelln (2015)

The transcription factors mentioned here are not the only mechanisms by which toxic metals affect thephysiology of brain cells. For example, Cheng et al. (2017) recently reported that the mechanisms underlyingaluminum(Al)-induced neurotoxicity and cell death in Alzheimer's disease dementia is mediated by the binding ofAl3+ to serum albumin, brain CK-B and 14-3-3ζ protein. The neurotoxicity and neurodegeneration induced by othertoxic metals such as cobalt, iron, molybdenum, nickel, uranium, fluoride, selenium, and silicon have been discussedelsewhere [reviewed in Killin et al. 2016]

microbiota in genetically engineered mice model of dementia. Similar results have been observed in human studies including clinical trials (Braniste et al. 2014; Cattaneo et al. 2017; Chiappelli 2018; Iemolo et al. 2009). These authors suggest that metabolic disorders may underlie changes in gut microbiota due to substantial decrease in *Bifidobacterium* and changes in *Enterococcaceae*, *Staphylococcus*, *Roseburia*, *Coprobacillus,* and *Dorea,* which in turn cause cognitive impairment and cerebral hypometabolism in neurodegeneration that characterize dementia.

The Microbiota–Gut–Brain Axis in Dementia

The connection between the gut and the brain was proposed since antiquity by the Greek philosophers and scientists (reviewed in Chiappelli 2018 and Welcome 2018). However, much attention was not given to this functional association not until the last century when several studies, using state-of-the-art tools began to report disordered gut functions occurring in patients with mental dysfunctions (Magni et al. 1991; Maguen et al. 2014; Mittermaier et al. 2004; Engel 1954; McKegney et al. 1970). The connection between the gut microbiota and the brain was fairly recently identified. The study that first reported a link between the gut microbiota and brain was conducted by Sudo and colleagues who reported stress response mediated by HPA axis and decreased BDNF levels in the hippocampus of germ-free mice (Sudo et al. 2004). Since then, there has been increased interest in investigating the association between the gut microbiota and brain functions in animals (Zheng et al. 2016; Neufeld et al. 2011; Huo et al. 2017) and humans (David et al. 2014; Sánchez-Villegas et al. 2009; Messaoudi et al. 2011; Romijn et al. 2017; Pinto-Sanchez et al. 2017) [reviewed in Ghaisas et al. 2016; Clark and Mach 2016; Lach et al. 2018; Wallace and Milev 2017] in both health and disease states. More recently, studies have revealed that gut microbiota disorder may underlie the development of dementia (Table 5). For instance, Araos et al. (2018) reported a strong association between dementia and dysbiosis of the gut microbiota in patients with dementia (Araos et al. 2018).

In a recent investigation by Cattaneo et al. (2017), it was shown that patients with Alzheimer's type dementia (who were positive for beta-amyloid proteins), had disordered gut microbiota, characterized by significant reduction in anti-inflammatory bacteria (*E. rectale*) and higher abundance of pro-inflammatory bacteria (*Escherichia/Shigella*), compared to healthy controls or patients who had cognitive impairment but were negative for beta-amyloid proteins (Cattaneo et al. 2017). Furthermore, levels of pro-inflammatory cytokines were higher in patients with Alzheimer's type dementia, compared to healthy controls or patients with cognitive impairment alone (Table 5; Cattaneo et al. 2017). The level of pro-inflammatory cytokines also positively correlated with inflammatory bacteria, but negatively correlated with the anti-inflammatory bacteria (Table 5; Cattaneo et al. 2017).

Recent report by Bäuerl et al. (2018) showed that the gut microbiota composition of Alzheimer's disease mice was similar to those of inflammatory gut disorders. There was an increase in inflammatory bacteria (Table 5) (Bäuerl et al. 2018). The gut-resident microbe *Cyanobacteria*

Table 5 List of original studies on influence of gut microbiota disorder on development of dementia

Study	Model	Description	Summary	Comments
Araos et al. (2018)	Humans	Case control	↑ *Clostridium difficile*	The authors observed substantial gut dysbiosis in dementia
Cattaneo et al. (2017)	Humans	Case control	↓ *E. rectale*, ↑ *Escherichia/Shigella*, ↑ IL-1β, IL-6, CXCL2, and NLRP3	Cytokines positively correlated *Escherichia* and *Shigella*, but negatively correlated with *E. rectale*
Vogt et al. (2017)	Humans	Case control	↓*Bifidobacteria*, including *B. fragilis,* and *Eubacterium rectale*	Decrease in the beneficial microbes of the gut correlated with cerebrospinal fluid biomarkers of Alzheimer's disease dementia
Bäuerl et al. (2018)	Transgenic APP/PS1 mice	Case control	↑*Proteobacteria*, particularly the genus *Sutterella* (*Betaproteobacteria*) and the inflammatory bacteria family *Erysipelotrichaceae*	During aging, *Turicibacteriaceae* (typical mice bacterial group) and *Rikenellaceae* increased in all groups, although total *Bacteroidetes* remained stable

can synthesize neurotoxins such as α-anatoxin, β-*N*-methylamino-L-alanine, saxitoxin, which may contribute to the development of dementia (Alkasir et al. 2017). Some gut residents *Citrobacter*, *Escherichia coli, Klebsiella*, *Mycobacteria*, *Pseudomonas, Streptococcus*, *Streptomyces, Staphylococcus, Salmonella*, and *Bacillus* species among others are capable of synthesizing amyloid peptides (e.g., curli fibers, CsgA, Aβ42) that are transported and deposited in the brain and may potentially cause cognitive impairment or dementia (Friedland and Chapman 2017; Welcome 2018). In addition, these amyloid proteins in the gut tend to destroy the protective defenses of the host by enhancing surface adhesion of pathogenic microbes and biofilm development (Alkasir et al. 2017). Decrease in the number of *Bifidobacteria*, including *B. fragilis,* and *Eubacterium rectale* correlate with cerebrospinal fluid biomarkers of AD (Vogt et al. 2017). Results of these studies raise important questions whether or not some microbes are responsible for causing dementia? Causative agents of dementia are yet to be identified (Chen et al. 2016). This may be one of the main reasons why there is currently no effective treatment of dementia as conventional strategies identify patients very late and treatment usually addresses symptoms and not the underlying causes (Alkasir et al. 2017; Iemolo et al. 2009). As a consequence, prevalence of dementia continues to increase worldwide (Scheltens et al. 2016).

Disordered Gut Microbiota is Associated with Dysfunctional Intestinal and Blood–Brain Barriers: Decrease in Gut Residents and Increase in Potentially Harmful Bacteria Enhances Dementia Development

One of the factors that aid the transport of toxigenic metabolites to the brain is the increased permeability of the intestinal and blood–brain barriers (Figs. 3, 4). Toxic metabolites such as *p*-cresol sulfate, indole-3 acetic, indoxyl sulfate, trimethylamine *N*-oxide, phenol- and sulfur-containing compounds as well as ammonia produced by the gut microbes can destroy the junctional protein complexes of the gut epithelium thereby increasing the leakiness of the gut epithelium (Awad et al. 2017; Coppo 2018; De Preter et al. 2006; Erdő et al. 2017; Fernandez-Prado et al. 2017; Förster 2008; Luettig et al. 2015; Rossi et al. 2015; Sawada et al. 2003; Tong and Hamel 1999; Wing et al. 2016; Zihni et al. 2016). This increases impairment in selective transport, paracellular shunt of substances between the gut and circulatory system, allowing for uncontrolled movement of proteins and lipids as well as ions and toxins into the surrounding tissues and circulatory system from the luminal side of the gut (Fig. 4) (Hu et al. 2016). Alhasson et al. (2017) recently showed that mice exposed to LPS have increased expression of claudin-2, which makes the gut epithelium leakier, thereby allowing toxins to translocate from the lumen into blood. In contrast, the expression of occludin was decreased in the small intestine (Alhasson et al. 2017). The authors also revealed that the LPS-exposed mice showed significant increase in TLR4 expression in small intestine and increase in inflammatory bacteria such as *Dorea*, *Allobaculum*, *Coprococcus*, *Ruminococcus,* and *Turibacter* (Alhasson et al. 2017). Similarly, there was increased secretion of IL-1β and monocyte chemoattractant protein-1, which are associated with inflammation (Alhasson et al. 2017). Human studies have reported similar findings in which gut inflammation was associated with increased expression of leaky intercellular protein (claudin-2) and decreased expression of occludins (Weber et al. 2008; Zeissig et al. 2007).

The toxigenic metabolites can also disrupt the endothelium of the blood–brain barrier (Fig. 4) due to disorder in the expression of sealing claudins which are supposed to preserve the permeability of the bloodbrain barrier (Amasheh et al. 2011; Awad et al. 2017; Braniste et al. 2014; Capaldo et al. 2017; Hoyles et al. 2018; Kelly et al. 2015). In addition, adherens proteins, membrane transporters, basal lamina, and extracellular matrix are affected (Erdő et al. 2017). Disorder

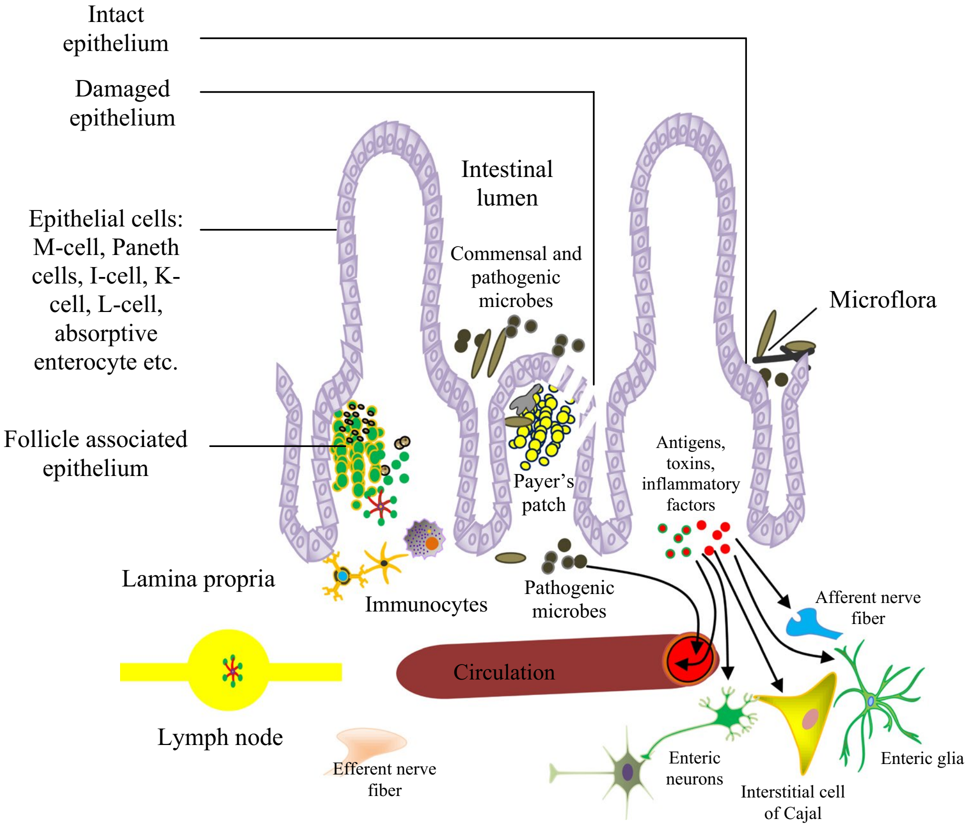

Fig. 3 The gut mucosa showing intact and defective epithelia resulting from pathogenic activity, which causes disorder in the sentinel system of the gut (mucous membrane, follicle associated epithelium, peyer's patch, lymph nodes, resident immunocytes). The defect or injury enhances translocation of pathogenic components, toxigenic metabolites and pro-inflammatory factors to different regions of the gut where they trigger local inflammatory response by activating immunocytes. The pathogenic microbes, toxigenic metabolites and pro-inflammatory factors can be transported via circulation to the brain (Bonfili et al. 2017; Welcome 2018). Furthermore the toxic metabolites and other substances released can stimulate the enteric brain, which comprises the enteric glia, the enteric neuron and the interstitial cells of Cajal, and also regulate the activity and synthesis machinery of neuroendocrine cells as well as afferent fibers of the vagus and spinal nerves of the gastrointestinal tract. The lymphatic vessels are also implicated in the inflammatory responses (Welcome 2018)

in the expression of sealing claudins and other membrane components increases the development of progressive cognitive impairment or dementia due to uncontrolled translocation of toxic metabolites into the brain, leading to loss of neurons, astrocytes, microglia, endothelial cells, and pericytes (Figs. 4, 5) (Erdő et al. 2017; Fang 2016; Hoyles et al. 2018). Indeed defects in blood–brain barrier components as well as glial cells have been observed in dementia (Chen et al. 2016; Ransohoff 2016). Using a mouse model, Alhasson et al. (2017) showed that altered gut microbiota resulted to intestinal injury and increased expression of leaky junctional proteins in the gut and activation of TLR4 as well as initiation of inflammatory process in the brain. Braniste et al. (2014) also reported that gut microbiota disorder resulted to low expression of the main tight junction proteins of the blood–brain barrier (ZO-1, occludin, and claudin-5) around the frontal cortex, hippocampus, and striatum in mice. Interestingly, it is well documented that these brain regions are involved in etiopathogenesis dementia (Kalaria 2016; Leverenz et al. 2009; Xu et al. 2012; Serrano-Pozo et al. 2011).

Increased production of toxic metabolites and pro-inflammatory cytokines by the activities of disordered gut microbiota has been implicated in local and systemic inflammatory responses that also involve the brain (Coppo 2018; Rossi et al. 2015; Wing et al. 2016; and reviewed elsewhere: Ho et al. 2015; Zhu et al. 2018). Pathological signaling of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α via the JAK-STAT (Janus kinase/signal transducers and activators of transcription) pathway in the brain can disorganize microtubule, via yet an unknown mechanisms that lead to dysfunctions of microglia, the main immune sentinels of the brain (Chio et al. 2013; Ghosh et al. 2013; Hickman et al. 2008; Millington et al. 2014). These microglia progressively loss the ability to clear cellular debris including amyloid proteins, which further stimulate signaling cascades that culminate in cell death (Ghosh et al. 2013; Millington et al.

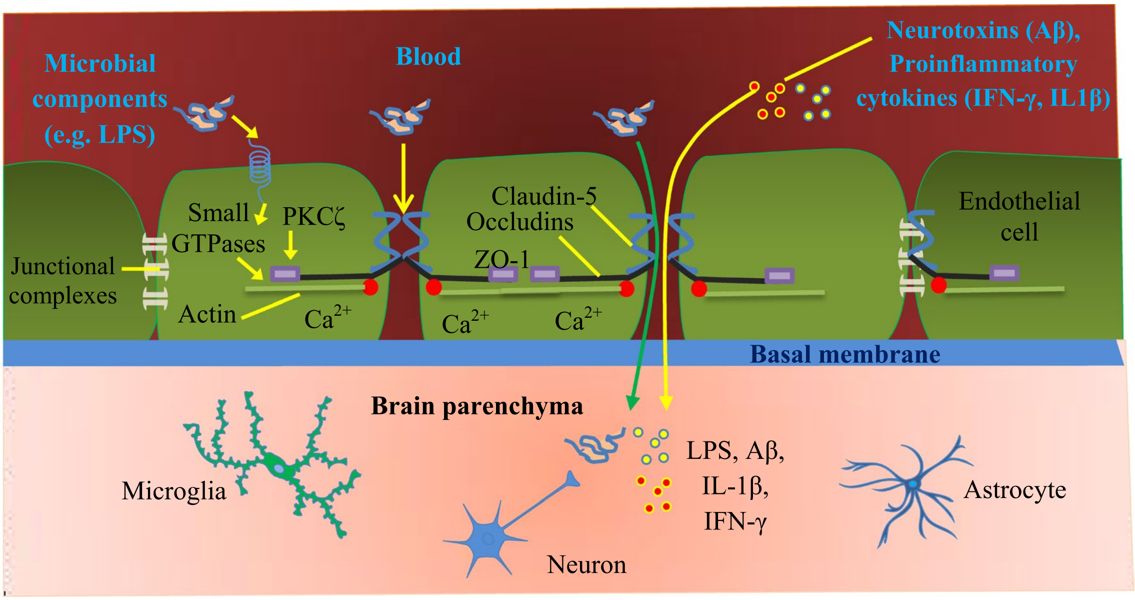

Fig. 4 Schematic representation of blood–brain barrier showing the action of pro-inflammatory factors: microbial components, neurotoxins (e.g., Amyloid beta polypeptide-Aβ), and pro-inflammatory cytokines (IFN-γ, IL-1β). These factors, when present in blood around the blood–brain barrier can trigger signaling pathways of the endothelial cells, activating small GTPases, protein kinases (e.g., atypical protein kinase-PKCζ), and elevation of cytosolic calcium that results to increased phosphorylation of cytoskeletal components (ZO-1, actin) that are associated with intercellular linkages of the endothelium. Furthermore, pathogenic substances and inflammatory factors (LPS, Aβ, IL-1β, and IFN-γ) can initiate endothelial secretion of proteases (e.g., matrix metalloproteinase), lipases, and carbohydrases into the extracellular matrix, which destroy ZO-1, claudin-5 and occludins of the blood–brain barrier, further increasing the permeability of the bloodbrain barrier. This promotes the movement of pathogenic substances and inflammatory factors (LPS, Aβ, IL-1β, and IFN-γ) from the blood into the brain parenchyma

2014). In the case of dementia due to Alzheimer's disease, the accumulating amyloid deposits provoke an inflammatory response that disorganizes the several protective mechanisms that favor neurodegeneration (Doens and Fernández 2014). In addition, signaling pathways that initiate gene transcription such as p38 and other protein kinases are activated (Ghosh et al. 2013). Furthermore, dysfunctions of amyloid peptide-degrading enzymes such as insulysin, neprilysin, and matrix metallopeptidase-9, have been reported in animal model of dementia (Hickman et al. 2008). All these processes lead to neurodegeneration which favor development of dementia or worsen the progression of the disease (Ray et al. 2016; Tóbon-Velasco et al. 2014).

Decrease in Beneficial Metabolites of the Gut-Resident Microbes is a Critical Underlying Factor for the Development of Dementia: Implications for New Therapeutics

The gut microbiota generates multiple biologically relevant molecules including biotin, folate, and SCFAs such as propionate, acetate, and butyrate, which modulate both peripheral and central processes to tissue or cellular injury (Lee et al. 2017; Russo et al. 2017). The gut microbiota metabolites are used locally by the epithelial cells of the gut or transported to different tissues and cells of the body via the circulatory system to exert an array of effects. Of particular interest are the SCFAs, which are metabolic products of the action of gut microbiota on certain carbohydrates that are non-digestible by the host cells (Lin et al. 2012; Tahara et al. 2018). These play a crucial neuromodulatory role on gut neuroendocrine cells and enterocytes, function as antioxidants, antitumorigens, chemotaxins, antimicrobial, and anti-inflammatory agents on the gut and distant tissues including the brain (Bonfili et al. 2017; Tan et al. 2014). Dementia and other neurodegenerative disorders including some gut diseases are characterized by significant decrease in the beneficial metabolites produced by the gut microbiota. Consequently measures that allow increase in these metabolites have found to enhance gut and brain functions in several diseases. For example, propionate was shown to stimulate intestinal gluconeogenesis, decrease stress and enhance memory. The SCFAs exert their effects on the host cells through the activation of G-protein-coupled receptors (GPR41, GPR43, and GPR109), located on the epithelial cells of the gut and brain endothelium (Tan et al. 2014; Hoyles et al. 2018). The free fatty acid receptors on colonic enteroendocrine cells are activated by the ligands, thereby stimulating the recruitment of

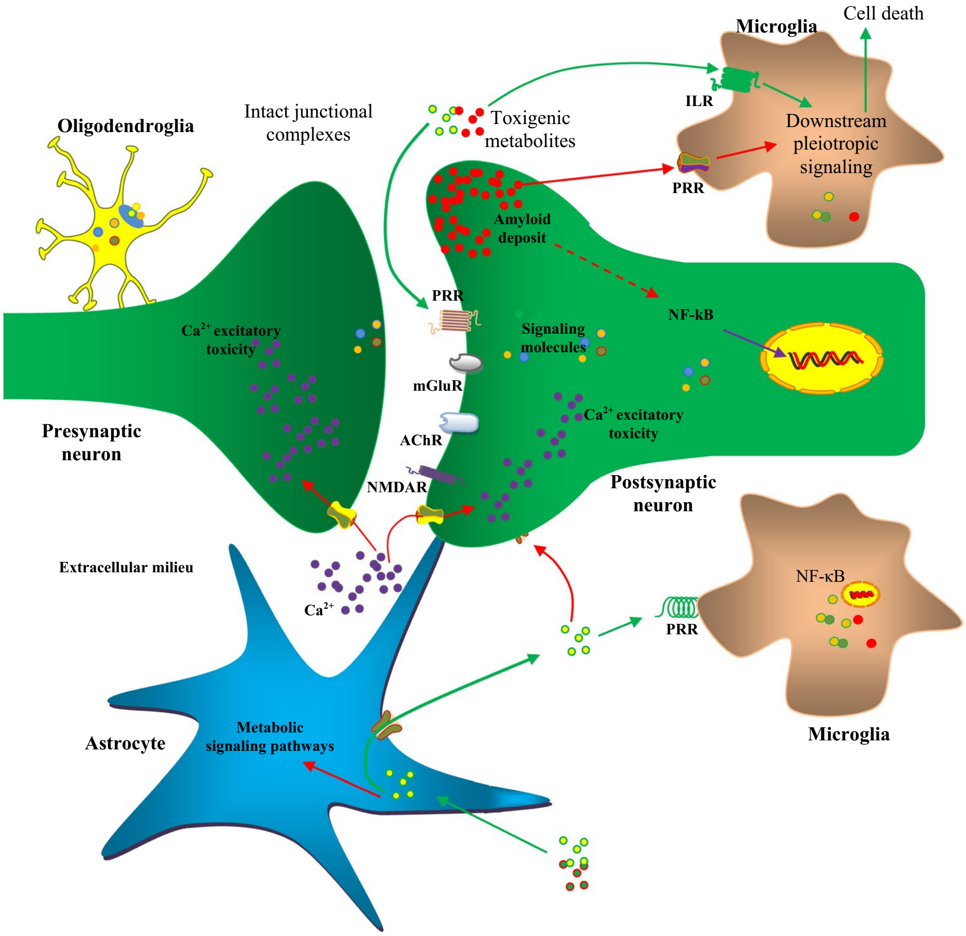

Fig. 5 Toxic metabolites or pro-inflammatory factors in the neuroglial circuitry mediating cognitive functions. The toxic metabolites and pro-inflammatory factors protein and lipid breakdown, mitochondrial dysfunction, disordered transport processes that culminate in neuroinflammation and neurodegeneration characterized for dementia (Browne et al. 2013; Chen et al. 2016; Streit et al. 2004). For instance, dysbiosis has been associated with increased circulating neurotoxic interleukin mediators, which in turn predispose to progressive cognitive impairment (Buford 2017; Chen et al. 2016). Furthermore aging is associated with increased circulating neurotoxic mediators such as TNF-α, IL-1β, IL-6, and C-reactive protein, which can directly cause low-grade inflammation, that predispose the individual to development of dementia (Buford 2017). The microbe-derived amyloids on the membrane of neurons, glia, epithelial cells can stimulate PRRs (pattern recognition receptors) such as TLRs causing local and possibly systemic inflammation, at least in part through their interaction with immune components of the brain (Friedland and Chapman 2017). As part of the toxic metabolites transported to the brain, amyloids can initiate series of intracellular signaling via activation of PPRs such as RAGE resulting to the activation of microglia (Yu and Ye 2015), phagocytosis of the amyloids (Li et al. 2015; Rangaraju et al. 2018). The binding of the metabolites or amyloids also initiate downstream signaling mediated via NF-κB pathways with resultant activation of the expression of pro-inflammatory cytokines resulting to neuroinflammation, excitotoxicity, and oxidative stress that lead to development of progressive cognitive impairment or dementia (Ray et al. 2016; Tóbon-Velasco et al. 2014)

synaptic or membrane vesicles loaded glucagon-like peptide 1, peptide YY, and other peptides towards the plasma membrane for exocytosis (Psichas et al. 2015). Furthermore, propionate can halt infections by controlling CD14 signaling, suppressing expression of low density lipoprotein receptor-related protein 1 and reduces oxidative stress via activation of the nuclear factor (erythroid-derived 2)-like 2, a guardian of human lifespan that protects against aging and diseases (Figarska et al. 2014; Hoyles et al. 2018, Lewis et al. 2010).

In the brain, SCFAs such as butyrate have been found to be substantially reduced in mice model of gut microbiota disorder (Braniste et al. 2014). Braniste et al. (2014) reported that decreased level of butyrate in the laboratory animals was not only associated with reduced expression of tight junction proteins of the blood–brain barrier, but also, neuroinflammation and cognitive impairment. Interestingly, administration of sodium butyrate, *Clostridium tyrobutyricum* (a bacteria that produces mainly butyrate) or *Bacteroides thetaiotaomicron* (a microbe that produces mainly acetate and propionate) to the laboratory animals resulted to increased expression of occludin in the frontal cortex and hippocampus (Braniste et al. 2014). Indeed previous studies have shown that SCFAs facilitating the assembly of tight junctions (Peng et al. 2007) and promote integrity of histo-hematological barriers (Mariadason et al. 1997, 1999).

Preclinical trials of prebiotics, probiotics, and synbiotics have shown promise for decreasing dysbiosis, and attenuating neuroinflammation and cognitive impairment. The effects of these substances are thought to be mediated via enteric nervous system, neuroendocrine system and vagus as well as spinal nerves of the gut (Akbari et al. 2016; Bambury et al. 2018; Daulatzai 2014). Probiotics such as *Lactobacillus paracasei*, *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus helveticus*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium infantis* enhance the central expression of BDNF, NMDA receptor and other peptides involved in synaptic and neural plasticity to improve memory, behavior, decrease anxiety, depression, and a range of neurological and psychiatric disorders (Ceccarelli et al. 2017; Chunchai et al. 2018; Hasan et al. 2016; Savignac et al. 2013).

Several randomized clinical trials in humans with progressive cognitive impairment or dementia have shown that consumption of beneficial microbes *Lactobacillus and Bifidobacterium* (Akbari et al. 2016; Santocchi et al. 2016; Akkasheh et al. 2016; Jamilian et al. 2016) or transplantation of fecal microbiota (Kang et al. 2017; Zhao et al. 2017) significantly decreased inflammatory markers and improved metabolic profile resulting to improvement in cognitive functions (Table 6). These clinical trials have indicated that great promise holds for application of the gut beneficial microbes for the treatment of dementia.

The beneficial effects of probiotics are due to their pleiotropic signaling capabilities. They interfere with a range of metabolic and cellular signaling pathways implicated in the maintenance of homeostasis. For instance, enhanced serum level of tryptophan, a precursor of serotonin, has been associated with oral probioticotherapy (Wang et al. 2016a). Furthermore, a crucial influence exerted by probiotics is due to increase in the number of gut commensals. Altogether, their effects culminate in improved endocrine, immune, neural signaling, carbohydrate, protein, and lipid metabolism, which have a summative effect in attenuation of neuroinflammation thereby preventing neurodegeneration (Westfall et al. 2017).

The prebiotics such as xylooligosaccharides, fructo-oligosaccharides, and galacto-oligosaccharides are non-digestible portion of carbohydrates ingested by the host, but under the influence of the gut microbiota, they confer a range of health benefits to the host. Like the probiotics, prebiotics improves memory and cognition, decrease anxiety, depression, and stress (Burokas et al. 2017; Savignac et al. 2013). Prebiotics are associated with decrease in microglial activation, improvement in brain mitochondrial function and hippocampal plasticity. The result is attenuation of neuroinflammation

Table 6 List of case report and randomized clinical trials on gut microbiota and cognitive impairment or dementia in humans

Study	Description	Result
Kang et al. (2017)	Randomized clinical trial involving daily maintenance dose of microbiota transfer therapy for 8 weeks (ClinicalTrials.gov, NCT02504554)	↑ *Bifidobacterium*, *Prevotella*, *Bacteroides fragiles*, and *Desulfovibrio*
Zhao et al. (2017)	Case report involving fecal microbiota transplantation with 400 ml of fecal suspension for 8 weeks	↑ cognitive functions, behavioral, vocal, and motor
Akbari et al. (2016)	Randomizeed, double-blind, controlled trial (IRCT201511305623N60) involving 200 ml/day probiotic milk supplementation containing *Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus casei, Bifidobacterium bifidum* (2×10^9 CFU/g for each) for 12 weeks	↑ cognitive functions and metabolic profile, ↓inflammatory markers
Santocchi et al. (2016)	Randomized controlled trial (ClinicalTrials.gov, NCT02708901) involving supplementation with the probiotic mixture "Vivomixx®"	↑cognitive and language functions, ↓gastrointestinal disorders
Akkasheh et al. (2016)	Randomized, double-blind, placebo-controlled clinical trial involving probiotic supplementation with *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) for 8 weeks	Improvement in metabolic profile, ↓depression, biomarkers of oxidative stress and inflammation
Jamilian et al. (2016)	randomized clinical trial was conducted among 60 pregnant women aged 18–37 years: probiotic supplementation with *Lactobacillus acidophilus, Lactobacillus casei,* and *Bifidobacterium bifidum* (2 × 109 CFU/g each) for 12 weeks	Improvement in metabolic profile, ↓ biomarkers of oxidative stress and inflammation
ClinicalTrials.gov (NCT03167983)	Clinical trial involving the effect of gut microbiota transplantation on dementia	Ongoing

and reduction in neurodegeneration (Chunchai et al. 2018). Thus prebiotics are therefore useful for neuroprotection (see list of prebiotics reviewed in Hang et al. 2016). Synbiotics are a combination of probiotics and prebiotics and have been found to exert profound beneficial influence on the functions of the gut and central nervous system (Chunchai et al. 2018).

Though there are several hypotheses on how pathogenic microbes colonize the gut (Houghteling and Walker 2015; Cong et al. 2017; Jacobson et al. 2018; Ribet and Cossart 2015), the mechanisms responsible for turning beneficial microbes into harmful ones that consequently predisposes to development of dementia are not clearly understood. To this end, in the next subsection, I discuss the molecular switches (from perspectives of epigenomics), controlling the change from beneficial to harmful gut microbiota and their impact on cognition and behavior (via signaling pathways). The molecular mechanisms responsible for the effects of oral bacteriotherapy and microbiota fecal transfer therapy on cognitive functions and behavior are also discussed.

Genetic and Epigenetic Factors May Play a Role in Controlling the Molecular Switches that Turn Beneficial Gut Microbiota to Harmful Species: Possible Molecular Mechanisms Mediating the Positive Effects of Bacteriotherapy in Dementia

Several changes in gene expression may be initiated by epigenetic modifications and not necessarily variations in genotype. These epigenetic modifications are caused by enzymes such as histone acetylases, histone deacetylases, DNA methylases, and DNA demethylases (Cenit et al. 2017; Bhat and Kapila 2017). The epigenetic enzymes participate in remodeling of chromatin and translation of coding mRNA into polypeptide chains (Cenit et al. 2017). Data indicate that non-coding RNAs are also involved in epigenetic modifications (Cenit et al. 2017).

Epigenetic modification is emerging as a critical missing link that shapes the gene, gut microbiota, and its functional relationship with the brain (Griñán-Ferré et al. 2018). Aging and environmental factors can change the epigenome of gut, microbiota, and brain cells (Saraswati and Sitaraman 2014; Buford 2017; Britton and McLaughlin 2013; Rayner and Horowitz 2013; Soenen et al. 2016), resulting to tremendous influences on the gut brain axis. Other confounding factors have been previously defined (Dunn et al. 2005). The changes can either promote cognitive decline or improvement (Griñán-Ferré et al. 2018). In case of cognitive decline, a couple of studies have reported that epigenetic mechanisms are involved in etiopathogenesis of dementia (Taskesen et al. 2017; reviewed in Veerappan et al. 2013; Maloney and Lahiri 2016). Indeed these mechanisms are currently known to be involved in regulation of memory and behavior, and development of cognitive disorders (Cenit et al. 2017).

The epigenetic modifications are influenced by microbial metabolites such as SCFAs, vitamins, polyamines, and polyphenols (Bhat and Kapila 2017). Indeed, SCFAs of the gut microbiota can inhibit histone deacetylates (enzymes that inhibit gene expression), thereby activating gene expression (Cenit et al. 2017). Sequencing analysis in humans has shown that DNA methylation is associated with predominance of *Firmicutes* (Kumar et al. 2014). Increase in the number of *Firmicutes* was related to gene methylation, and also, linked to inflammatory responses (Kumar et al. 2014). Similar findings have been documented by other researchers (Bhat and Kapila 2017; Remely et al. 2014a,b). Certain genetic and epigenetic marks on the host cells caused by the gut microbiota are responsible for triggering the onset of inflammatory responses and regulating metabolic functions, which in turn affect behavior and cognitive functions (Bhat and Kapila 2017). Elsewhere, Remely et al. (2014) showed that the gut microbiota regulate inflammatory responses by altering the epigenetic information related to TLRs. Specifically, inflammation seems to increase the number of methylation of 5′-cytosine-phosphate-guanine-3′ sites in specific promoter region of TLR2 (Remely et al. 2014a,b).

However, microbial species inhabiting the gut are also dependent on certain genetic and epigenetic modifications (Bonder et al. 2016; Canani et al. 2011). So, some genetic information or epigenetic modifications can substantially affect the composition and types of microbes inhabiting the gut (Bonder et al. 2016). In a genome-wide analysis, Bonder et al. (2016) studied the effects of host genetics on microbial species, pathways, and epigenetic modifications in 1514 persons, and showed that 9 and 33 gene loci were associated with microbial species and microbial pathways respectively. Bonder et al. (2016) also reported influence of gene-diet interaction on the predominance of *Bifidobacterium* sp. Although no specific bacterial species has been closely associated with development of dementia, the pathways, metabolic changes, and inflammatory responses mediated by disordered microbiota in the gut epithelium and blood–brain barrier are believed to be the major factors that underlie the development of dementia (Davenport et al. 2015; Canani et al. 2011).

The positive effects of bacteriotherapy in enhancing cognition and behavior, and improving metabolic profile in dementia may be due to epigenetic modifications elicited by increased synthesis of beneficial gut microbiota metabolites such as SCFAs (Canani et al. 2011). Using transgenic mice model of Alzheimer's disease type dementia, Bonfili et al. (2018) demonstrated that probiotics formulation decreased oxidative stress in brain through activation of SIRT1 (sirtuin-1), a nicotinamide adenine dinucleotide-dependent deacetylase, involved in epigenetic modifications in multiple organs and tissues including the brain and gut (Bonfili et al. 2018). Braniste et al.'s (2014) data revealed that administration of sodium butyrate to mice with disordered gut microbiota resulted in an increase in histone acetylation in the brain (Braniste et al. 2014). Like other SCFAs, butyrate inhibits histone deacetylase, and also, functions as a ligand for some G-protein-coupled receptors (Braniste et al. 2014). Furthermore, it is an essential energy metabolite, required for normal physiological processes (Braniste et al. 2014). The receptors for SCFAs are also influenced by epigenetic modifications, especially during inflammatory reactions, initiated by the gut microbiota (Remely et al. 2014a,b). In a mice model of Alzheimer's disease type dementia, Bonfili et al. (2017) showed that feeding with probiotic formulation led to improvement in the composition of gut microbiota and its metabolites, which were associated with substantial decrease in plasma pro-inflammatory cytokines and major metabolic hormones used as therapeutic targets in neurodegeneration. Probiotic feeding, which resulted to enhancement of beneficial population of gut microbiota was associated with improvement in cognition and reduction in brain damage due to reduced accumulation of amyloid beta peptides and other neurotoxins (Bonfili et al. 2017).

Signaling Pathways, Mediating the Effects of Gut Microbiota Activity on Cognition and behavior

The harmful effects of gut microbiota disorders on the cognition and behavior are achieved via signaling pathways. Similarly, the effects of bacteriotherapy on the brain occurs through these signaling pathways, which form a functional link between the gut microbiota and the brain and comprises neuroendocrine, neural, neuroimmune signaling pathways. The endocrine pathway is mediated by the interaction between the gut microbiota and neuroendocrine cells of the gut. The neural pathway is mediated by interaction of the gut microbiota with central nervous system (including hypothalamic–pituitary–adrenal axis, HPA axis), autonomic nervous system (via the vagus nerve and the sympathetic fibers), and enteric nervous system. The immune pathway is due to the interaction between the gut microbiota and neuroimmune substances (Dinan and Cryan 2017; O'Mahony et al. 2015; Thakur et al. 2014).

The metabolites of the gut microbiota such as SCFAs, gamma amino butyric acid (GABA), serotonin, norepinephrine, histamine etc. regulate a range of physiological processes in the gut and brain via their interaction with neuroendocrine, neural, and neuroimmune signaling (Cristiano et al. 2018; Dinan and Cryan 2017).

Gut Microbiota-Neural Signaling

The gut alone synthesizes over 60 types of transmitter molecules that not only influence gut functions, but also nervous system activity. Thus dysfunctions in the gut homeostasis can result to disorder in synthesis of the gut neurotransmitters, neuropeptides, hormones, and immunomodulators, which can affect the gut–brain axis (Welcome 2018). Some of the gut derived hormones can affect the functions and composition of the gut microbiota. Surprisingly, not only the gut cells synthesize these neurotransmitters, neuropeptides, hormones, and immunomodulators, but also the gut microbiota (Welcome 2018). Furthermore the gut microbiota can trigger the synthesis of these molecules from epithelial neuroendocrine cells of the gut. So, the cholinogenic gut microbe, *Lactobacillus* sp. produces acetylcholine that affects vagal, neuroendocrine and neuroimmune signaling. *Bacillus* sp. is dopaminergic (Alkasir et al. 2017). The gut microbiota regulates the HPA axis by release of cortisol, which may affect microglia activation, and cytokine release, homing of distant and local immunocytes to the site of cerebral aggression. The gut microbiota can affect long term potentiation (important factor in memory formation and cognitive processes) via its interaction and regulation of GABA, *N*-methyl-D-aspartate (NMDA) receptor, postsynaptic density marker 95 (PSD-95), and brain-derived neurotrophic factor (BDNF) (Wang et al. 2016b; Yoshiike et al. 2008).

Gut Microbiota-Humoral Signaling

Endocrine pathway represents a crucial bidirectional link between the gut microbiota and brain structures that allows the transfer of humoral factors, which mediate a range of brain activities including cognition (Clarke et al. 2014; Farzi et al. 2018). Gut derived hormones regulate energy homeostasis, and exert considerable influence on the enteric nervous system, central nervous system, modulating cognitive functions and behavior (Bonfili et al. 2017; Chiappelli 2018; Welcome 2018).

Growth hormones protect neurons from toxicity and excessive excitatory signaling (Mattson et al. 1993) in part by stabilizing Ca^{2+} signaling, stabilizing the expression and NMDA and GABA receptor mediated signaling (Mattson et al. 1993; Welcome 2018). In addition, adequate humoral signaling exerts protective effects on the mitochondria. This way, growth factors prevents neurodegenerative processes that result to dementia (Bonfili et al. 2017). Furthermore, the gut synthesized hormones leptin, ghrelin, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide confer neuroprotective effects against neurotoxicity induced by harmful pathogenic microbial toxins (toxigenic metabolites) (Bayliss et al. 2016; Mattson et al. 1993; Shen et al. 2017). Consequently, application of analogs of these hormones can be helpful in the treatment of cases of dementia.

Conclusion

The gut microbiota is a diverse population of beneficial microbes that coordinate several cellular signaling pathways and a range of metabolic processes via multiple mechanisms involving neural, immune, and neuroendocrine pathways. These pathways constitute a crucial means by which the gut microbiota communicates with the brain. However, the gut-resident microbes are affected by several factors, which may lead to decrease in the composition of the beneficial microbes. The gut microbiota plays a critical role in the etiopathogenesis of dementia. The association between disorder of the gut microbiota and dementia can be highlighted by the peculiar role of the metabolic products of the gut-resident microbes together with their specific roles in the maintenance of both the intestinal and blood–brain barriers as well as regulation of local, circulating and distant immunnocytes, enteric, visceral, and central neural functions. The molecular switches that control the composition of gut microbiota, functional integrity of gut epithelial, and blood–brain barriers are mediated by genetic and epigenetic imprints that determine the state of both gastrointestinal and brain functions. Certain epigenetic marks can result to gut microbiota disorders that subsequently predispose to gut epithelial and blood–brain barrier dysfunctions, underlying the onset of dementia. Further research that will address these epigenetic marks may provide important cues for potential therapeutic targets for dementia.

Compliance with Ethical Standards

Conflicts of interest There is no conflict of interest regarding the publication of this paper.

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