Ageing Research Reviews 70 (2021) 101396

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The neuromicrobiology of Parkinson's disease: A unifying theory

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ARTICLE INFO

Keywords:
Age-related Parkinson's disease
Infection
Bacteria
Mitochondria
Gut-brain axis
Gut microbiome
Inflammation

ABSTRACT

Recent evidence confirms that PD is indeed a multifactorial disease with different aetiologies and prodromal symptomatology that likely depend on the initial trigger. New players with important roles as triggers, facilitators and aggravators of the PD neurodegenerative process have re-emerged in the last few years, the microbes. Having evolved in association with humans for ages, microbes and their products are now seen as fundamental regulators of human physiology with disturbances in their balance being increasingly accepted to have a relevant impact on the progression of disease in general and on PD in particular. In this review, we comprehensively address early studies that have directly or indirectly linked bacteria or other infectious agents to the onset and progression of PD, from the earliest suspects to the most recent culprits, the gut microbiota. The quest for effective treatments to arrest PD progression must inevitably address the different interactions between microbiota and human cells, and naturally consider the gut-brain axis. The comprehensive characterization of such mechanisms will help design innovative bacteriotherapeutic approaches to selectively shape the gut microbiota profile ultimately to halt PD progression. The present review describes our current understanding of the role of microorganisms and their endosymbiotic relatives, the mitochondria, in inducing, facilitating, or aggravating PD pathogenesis.

1. Introduction

Parkinson's disease (PD) is currently the second most common neurodegenerative disease whose incidence is expected to increase in the upcoming decades due to the extension of life expectancy (Kontis et al., 2017). The symptoms associated with this disease were first described in 1817 by James Parkinson, whose observational study entitled "Essay on the Shaking Palsy" reported several patients with motor impairment that included tremor at rest, bradykinesia, muscular rigidity and postural instability (Parkinson, 2002). It is currently known that motor impairment is the result of dopamine (DA) deficiency originating from a progressive loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) (Tolosa et al., 2009). Other symptoms, often preceding motor impairment by many years, have also been associated to PD, namely olfactory loss, sleep disturbance, depression and gastrointestinal (GI) dysfunction (Cardoso and Empadinhas, 2018). However, 200 years after James Parkinson's first observational study, the PD aetiology remains unknown.

Although most cases of PD occur in a sporadic manner, a minor subset of PD cases is inheritable and attributable to mutations in genes associated to disease-linked loci PARK, including *SNCA*, *Parkin*, *DJ-1*, *PINK1* and *LRRK2*. Many theories have been proposed for the aetiology of idiopathic PD (Johnson et al., 2019; Kalia and Lang, 2015; Langston, 1989) but none provide solid ground to explain all the symptoms. Indeed, several authors insightfully consider PD as a syndrome with different possible aetiologies (Kempster et al., 2017; Obeso et al., 2017; Titova et al., 2017). This plausible explanation is not new, having been suggested in the beginning of the 20th century (Compin, 1902). Under this perspective, PD is a multifactorial disease that can have multiple aetiologies and where different players converge to trigger, facilitate or aggravate its progression in genetically susceptible individuals, some of which with identified mutations or polymorphisms in specific genes (Johnson et al., 2019; Santos and Cardoso, 2012). Indeed, most mutations reported in familial PD patients congregate into harmful inflammatory responses and mitochondrial disfunction (Dionísio et al., 2019; Frank-Cannon et al., 2008; Quinn et al., 2020). At least 16 familial PD-linked genetic loci were identified to date (PARK1−16, including *SNCA*, *Parkin*, *DJ-1*, *PINK1*, *NURR1*, *OMI/HTRA2* and *LRRK2*) (Cardoso,

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https://doi.org/10.1016/j.arr.2021.101396
Received 12 April 2021; Received in revised form 11 June 2021; Accepted 19 June 2021
Available online 23 June 2021

2011). Individuals with mutations in these genes share symptomatology with idiopathic PD cases at an early stage of disease progression (Santos and Cardoso, 2012). However, some authors reported an incomplete penetrance in patients with some PD-linked mutations (Johnson et al., 2019), which suggests that genetically susceptible individuals will still require a environmental trigger to develop PD (Johnson et al., 2019). Therefore, different aetiologies, namely gene mutations, infection, protein misfolding and mitochondrial dysfunction, acting independently or combined, are probable causes of PD onset, a concept recently referred to as the "multiple hit hypothesis" (Patrick et al., 2019). Manifestation of idiopathic PD will also depend on several factors, such as individual nuclear/cytosolic protein variants, endosymbiont mitochondria and microbes that will synergically contribute to disease development (Cardoso and Empadinhas, 2018; Johnson et al., 2019).

2. An historical perspective of the "infectious PD"

Since its discovery, the possible aetiology of PD has changed along the years. In the beginning, PD was suspected to result from traumatism or triggered by an infectious agent. However, new scientific breakthroughs emerging in the 20th century uncovered other more plausible causes of PD. The evidence that protein misfolding, neuroinflammation or mitochondrial dysfunction among others were related to the pathophysiology of the disease decreased the interest in an infectious aetiology of PD. However, most recent evidence sustains the important role that microorganisms actively play in the development and progression of PD. New data suggest that bacteria can indeed be the initial trigger of some neurodegenerative diseases, including PD. Although this perspective is actually quite old, the new approach is not substantiated on the classical infectious nature of microbes. The suspicion about a microbial involvement in dopaminergic degeneration is as old as its discovery. Indeed, James Parkinson perceptively hypothesized that "inflammation, or rheumatic or scrophulous affection" (a tuberculosis (TB) manifestation at the cervical lymph nodes) located near the medulla oblongata could be the origin of PD symptoms. This allegation was quite accurate considering the limited knowledge available at that date, that the aetiological agent of TB would only be revealed 65 years later by Robert Koch (Koch, 1882), and even that the role of SNpc in the control of movement was unknown. Only much later, researchers from Charcot's school at Salpêtrière Hospital confirmed the presence of tuberculoma in many patients with resting tremor and impaired posture and balance (Blocq and Marinesco, 1893; Hostiuc et al., 2016), in that way disclosing a possible anatomical association between TB and PD (Hostiuc et al., 2016). A few years later, and based on Blocq and Marinesco's findings, Brissaud also suggested that the particularly affected area was the "Locus Niger", now known as *substantia nigra* (SN) (Brissaud, 1895).

Later discoveries progressively pointed to a clear link between microbial infection and PD symptoms, one emerging from the epidemic outburst of encephalitis lethargica in the first decade of the 20th century. The initial symptoms of encephalitis lethargica namely fever, somnolence, and oculomotor abnormalities were often confused with influenza-like symptoms. However, postencephalitic patients usually developed a chronic phase characterized by parkinsonism that appeared months or years later (Ravenholt and Foege, 1982; von Economo, 1918). Based on the contemporary Spanish influenza pandemic, many authors suggested that encephalitis lethargica and influenza might share the same infectious agent as trigger (Hoffman and Vilensky, 2017; McCall et al., 2008). Anatomic findings evidenced that the surviving nigral brain cells in patients with postencephalitis accumulated aggregates later known as Lewy bodies (LBs), showing severe cellular degeneration of SN (Tretiakoff, 1919). In the early XX century two vaccines were developed based on an infectious origin. Encephalitis lethargica patients used to be treated with a vaccine generated from dead bacteria of the species *Streptococcus viridians* (Rosenow, 1923) or from immunized rabbit serum infected with the virus *Herpes simplex* (Neal and Bentley, 1932). Although the therapeutic efficacy of the bacterial trials was at the most doubtful, it seemed that the viral vaccine showed better results (Louis, 2002). However, the possibility of encephalitis lethargica being caused by a virus was later discarded because viral RNA was not found in postencephalitic parkinsonian brain material (McCall et al., 2008). Although a century has passed and a possible role for an infectious agent in encephalitis lethargica is still controversial (Hoffman and Vilensky, 2017), the most recent findings indicate that this condition could be the result of an autoimmune response against neurons (Dale et al., 2004; Hoffman and Vilensky, 2017).

From that date forward and over many years, other pathogens such as human immunodeficiency virus (HIV), viruses associated with unspecific encephalitis namely Influenza A, Japanese fever virus, Epstein-Barr virus (EBV), and even some bacteria of the genera *Mycobacterium*, *Nocardia*, *Borrelia* or *Listeria*, most of which associated to infectious diseases ranging from tuberculosis to Lyme disease or foodborne illness, have been suggested to trigger or somehow be linked to PD (Limphaibool et al., 2019). The current point of view postulates that microorganisms may indeed actively participate in PD progression, but not embedded in the classical infectious paradigm postulated by Robert Koch.

3. Microbial infection of the brain

The first pathogen to be associated with PD was *Mycobacterium tuberculosis* (*Mtb*) known to cause tuberculosis (TB), the leading cause of annual deaths from a single infectious agent, surpassed in 2020 by SARS-CoV-2 causing COVID-19 (Johns Hopkins University of Medicine, 2021; Koch and Mizrahi, 2018; Wilkinson et al., 2017). Key to *Mtb* pathogenesis is its intrinsic ability to reside inside the host macrophages, for long periods of time and up to several decades (Koch and Mizrahi, 2018). Within the macrophage, *Mtb* is able to inhibit lysosomal activity and prevent inflammasome activation (de Martino et al., 2019), which enables the bacteria with a strategy to evade immune system surveillance. A retrospective cohort study showed that patients with active TB have a 1.38-fold higher risk of developing PD (Shen et al., 2016). Indeed, some cases of TB are associated with the development of meningitis associated with significant motor alterations (Alarcón et al., 2000). Up to 21 types of neurological manifestations have been reported in TB patients, some were considered syndromes, one of which being parkinsonism (Udani et al., 1971). However, TB may occur with or without meningitis (Pandey and Singh, 2017; Pandita et al., 2015; Sanei Taheri et al., 2015). Brain parenchymal involvement usually presents as tuberculoma, the most common lesion in central nervous system (CNS) tuberculosis (Kim et al., 1995; Sanei Taheri et al., 2015), with similarities to pyogenic bacterial infection on neuroimaging studies (Sanei Taheri et al., 2015). The disease can also cause cerebritis, cerebral abscess, miliary (disseminated) TB, or encephalopathy (Sanei Taheri et al., 2015). Although parkinsonism-like manifestations may sometimes be delayed after a previous TB infection and tuberculoma diagnosis (Pandey and Singh, 2017), it is also possible that no previous clinical manifestation of TB infection is detected in both immunocompetent and immunosuppressed patients (de la Fuente-Aguado et al., 1996; Haddadian et al., 2004; Pandita et al., 2015).

The mechanisms underlying the induction of parkinsonism in humans by *Mtb* remain unknown, *in vitro* exposure of *Mtb* to purified human microglia and astrocytes showed selective infection of microglia (Pfyffer et al., 1996) mediated by CD14 receptor (Rock et al., 2004). In the case of human monocytes-derived macrophages, CD14 did not mediate cellular entry of *Mtb* although it was upregulated in mononuclear phagocytes (Shams et al., 2003).

Intracerebral injections of different *Mycobacterium* species in murine models induced neuroinflammatory responses with lymphocytic infiltration and microglia activation around the meninges and the perivascular area (Mazzolla et al., 2002; van Well et al., 2007). However, while *Mycobacterium bovis* was able to grow in murine cerebrospinal fluid (CSF) (Mazzolla et al., 2002), *Mtb* was not detected in the CSF (van

Well et al., 2007), showing elevated levels of chemokines but not any alteration in CSF cytokine content nor evidence of meningitis (van Well et al., 2007).

Remarkably, some of the genes whose mutations are related to familial cases of PD, such as *Parkin* (PARK2 locus), have also been described as important players in TB. *Parkin* gene polymorphisms have been associated with the increased susceptibility to infections by intracellular bacterial pathogens, such as *Mycobacterium* spp. and *Salmonella* spp. (Ali et al., 2006; Cambri and Mira, 2018). *Parkin*-deficient mice were not able to eliminate mycobacteria from macrophages, indicating Parkin plays a role in innate immune defence (Manzanillo et al., 2013). Furthermore, genomic studies in humans reported that LRRK2 (PARK8 locus) is involved in the immune response to *Mycobacterium* infection (Herbst and Gutierrez, 2019; Wang et al., 2018; Zhang et al., 2009). LRRK2 is a known risk factor for inflammation and infection by intracellular pathogens (Fava et al., 2016; Herbst and Gutierrez, 2019) and its inhibition targeted *Mtb* to phagolysosomes (Gutierrez et al., 2004). Additionally, a LRRK2-dependent mechanism to control *Mtb* replication by the upregulation of phagosome maturation has been described (Härtlova et al., 2018).

Another intriguing observation linking TB to PD through the immune system is that MPTP-treated mice previously vaccinated with BCG Bacillus Calmette-Guérin, a strain of Mycobacterium bovis preserved striatal dopamine integrity and showed no signs of microglia activation in the SN, which suggested that BCG vaccination induced neuroprotection by peripheral immune stimulation (Yong et al., 2011). Moreover, some PD drugs such as tolcapone and entacapone have been shown to have anti-TB activity (Kinnings et al., 2009). Despite these inspiring correlations between *Mtb* infection, the immune system and PD seem to suggest a potential role for the pathogen in PD, the underlying mechanisms are still unknown and further studies are required to elucidate these intriguing observations.

In addition to *Mtb*, other bacterial infections can also induce parkinsonism-like symptoms. Members of the genus *Nocardia* are closely related to mycobacteria as they belong to the same order of the phylum Actinobacteria and both groups have clinically relevant members (Roberts, 1985). *Nocardia* and *Mycobacterium* strains are not easily distinguished by classical culturing methods nor serologically and only molecular methods can readily separate them (Dong et al., 2019). Several animal models of *Nocardia* spp. infection showed interesting clinical and neuropathological similarities to PD (Gorrill, 1956; Kohbata and Beaman, 1991; Loeffler et al., 2016; Smith and Hayward, 1971). Intravenous administration of *Nocardia asteroides* in BALB/c mice showed bacterial growth in the pons, in the SN, in the hypothalamus and in the thalamus 24 h after injection (Beaman, 1993). *Nocardia* cells were detected in the endothelium, glia, neurons and axons, where they induced axonal degeneration sometimes involving the transition to a cell wall defective form (L-form) (Filice et al., 1980; Kohbata, 1998), contributing to a defective inflammatory response (Beaman, 1993). Still, some reports argue that *Nocardia* were not completely inert because neurons showed some signs of degeneration (Beaman, 1993). Other studies also showed that *Nocardia* was able to deplete DA by DA-depleting toxin secretion both *in vitro* (Loeffler et al., 2004) and *in vivo* (Hyland et al., 2000; Kohbata et al., 1998; Loeffler et al., 2016). Furthermore, *Nocardia* infection could induce motor alterations that emerged even after its apparent elimination from the brain (Kohbata, 1998; Kohbata and Beaman, 1991). Though, some authors suggest that movement dysfunction observed in *Nocardia*-infected mice could be caused by inner ear pathology and not due to SN degeneration (Loeffler et al., 2016). In addition, the attempt to detect *Nocardia* by serological methods or by hybridization *in situ* techniques in PD patients' brain tissue were unsuccessful (Hubble et al., 1995; Kohbata and Shimokawa, 1993) or at least controversial. Some authors found *Nocardia*-specific 16S ribosomal ribonucleic acid (RNA) in the SN of PD patients (Chapman et al., 2003), but others failed to replicate the results (Lu et al., 2005). Monkeys infected with a strain of *Nocardia asteroides* developed motor abnormalities (Loeffler et al., 2016) and *post-mortem* analyses revealed that their brains showed α-synuclein (Asyn) and ubiquitin-positive intraneuronal inclusions that were positive for *Nocardia* 16S RNA (Loeffler et al., 2016). Although these data were from animal models infected by IV injection and the most common route of *Nocardia* entry is by inhalation or through breaks in gut mucosa (Tsushima et al., 2000), these observations are important and warrant new studies to decipher the mechanisms of *Nocardia* infection *per se* and also in the context of PD.

Other pathogenic bacteria that have been associated to motor dysfunction are *Borrelia burgdorferi* and *Treponema pallidum*, the aetiological agents of Lyme disease and syphilis, respectively, and which belong to the order Spirochaetales (Radolf et al., 2016; Zhang et al., 1997). These bacteria survive as obligate intracellular parasites within the host cells for long time evading the immune response (Auwaerter et al., 2004). In the case of Lyme borreliosis, the spirochete is inoculated through bites of ticks of the genus Ixodes. Initially, *B. burgdorferi* activates local inflammation, the outer surface protein C (OSPc) binds plasminogen activating plasmin and complement. Plasmin induces tight-junction breakdown by collagenase and matrix metalloproteinases (MMPs) activation, which help spirochetes disseminate fast to the entire body (Auwaerter et al., 2004; Toledo et al., 2012). *B. burgdorferi* can also adopt the L-form phenotype enabling it to be more evasive to immune system surveilance (Rudenko et al., 2019). Clinical manifestations are variable and can involve motor alterations that include abnormal gait, impaired movement and motor planning or shaking palsy (Mygland et al., 2010; Wormser et al., 2006). Epidemiological studies associated *B. burgdorferi* with PD (Bu et al., 2015), however other authors reject this possibility because the absence of positive correlation between geographical distribution of Lyme disease and PD cases (Forrester et al., 2015).

Treponema pallidum is usually transmitted by human sexual activity and its mechanisms of infection are very similar to those of *Borrelia burgdorferi* (Blum et al., 2017; Porcella and Schwan, 2001). Syphilis may present symptoms common to other diseases and can be characterized by having 4 different manifestations: primary, secondary, latent or tertiary, the latter designated neurosyphilis if neurological symptoms are present. Neurosyphilis continues to have a significant clinical incidence being that symptomatology may be confused with movement abnormalities similar to PD, although they have been considered quite rare (McAuley and Hughes, 2015; Sabre et al., 2016; Spitz et al., 2008; Yin et al., 2015). Since movement alterations improved with penicillin G treatment (McAuley and Hughes, 2015; Sabre et al., 2016; Spitz et al., 2008), it was suggested that the aetiology was probably linked to the pathogenic agent (Spitz et al., 2008). However, a case-study reported that in spite of antibiotic treatment initially ameliorated the parkinsonism symptoms, the patient slowly deteriorated in a fashion similar to idiopathic PD 15 years later, possibly indicating co-occurrence of both pathologies (McAuley and Hughes, 2015). Identification of *T. pallidum* in patients is extremely difficult once the infection is disseminated because the number of spirochetes detected is very small, even in patients with chronic infection. Additionally, PCR detection has a high rate of false negatives especially in CSF samples (Exner and Lewinski, 2003; Guy and Stanek, 1991; Lebech and Hansen, 1992).

4. Mitochondrial dysfunction – an odd case of "infection"

Mitochondria are key players in the development of PD (Cardoso, 2011) not only due to the loss of function in terms of ATP production, calcium buffering capacity and intrinsic apoptosis activation, but also as mediators of innate immunity activation (Cardoso and Empadinhas, 2018). Mitochondria are evolutionary descendants of endosymbiotic Proteobacteria (Gray, 2017; Martijn et al., 2018) thus sharing multiple molecular determinants with their free-living relatives. Both the matrix of mitochondria and the cytosol of bacteria contain DNA, tRNA, ribosomes, and numerous soluble enzymes; both reproduce by binary fission

and bear a N-formylmethionine residue in their proteins' N-terminal. Remarkably, some bacterial pathogen-associated molecular patterns (PAMPs) such as formyl peptides persist in mitochondria and activate formyl peptide receptors, and unmethylated CpG dinucleotides that signal toll-like receptors (TLR) involved in the innate immune system activation. Therefore, the innate immune system does indeed recognize mitochondrial motifs, also called damage-associated molecular patterns (DAMPs). Upon mitochondrial exposure of DAMPs a sterile inflammation is activated that mimics the response to infection (Pallen, 2011). It was recently described that mitochondrial DAMPs induced a mitochondria-specific autoimmune response that could ultimately lead to neuronal death and PD (Matheoud et al., 2019, 2016). This provides the mitochondria a central role in innate immunity activation (West et al., 2015). It was also recently described that the release of mtDNA in the cytoplasm activates the innate immune system, inducing an antimicrobial response and inflammatory pathology (Dhir et al., 2018; West et al., 2015; Zhao et al., 2019). mtDNA can be recognized by a double-stranded DNA sensor, acting in a similar way as pathogen-derived nucleic acids are sensed by the host during infection and also triggering protective immune responses (Zhao et al., 2019). This activates IFN-1-mediated immune response through the STING-TBK1-IRF-3 signaling axis (Zhao et al., 2019). Indeed, the loss of Parkin and Pink1 in mice with mitochondrial stress led to the activation of innate immunity mediated by DAMPs, which caused dopaminergic neuron loss and motor impairment, alterations that could be rescued by the inhibition of STING-mediated type I interferon response (Sliter et al., 2018).

Additionally, mutations in Parkin and LRRK2 associated with Type-1 reactions (T1R), which are a pathological immune response in leprosy, were also enriched in PD patients, revealing that neuroinflammation in PD and peripheral nerve damage due to T1R activation share overlapping genetic control of pathogenicity (Fava et al., 2019). These studies suggest that the trigger of infectious Parkinsonism may be similar to that of idiopathic and genetic PD. However, the underlying mechanisms remain unknown. It is well known that LRRK2 plays a role in immune responses triggered by infectious agents, which may potentiate neurodegeneration (Brockmann et al., 2016; Herbst and Gutierrez, 2019). In addition to LRRK2, PINK and Parkin are also highly expressed in macrophages and in microglia (Brockmann et al., 2016) where their mutation can induce mitochondrial dysfunction altering microglia and enhancing neuroinflammation (Botta-Orfila et al., 2012; Dionísio et al., 2019; Frank-Cannon et al., 2008; Lee and Chung, 2012; Moehle et al., 2012; Quinn et al., 2020; Sun et al., 2018a, 2018b; Torres-Odio et al., 2017)

Since progressive mitochondrial pathology, a main feature of both genetic and idiopathic PD, leads to the exposure of DAMPs mimicking microbial infection, we sought to reconcile infection-triggered with idiopathic and genetic PD cases and wonder if the PD syndrome can indeed be an infectious disease caused by "pathogenic" mitochondria.

5. Microbial impact in the brain

Humans evolved in a microbial world characterized by a broad range of different and permanent interactions (mutualism, commensalism or symbiosis) toward the adaptation to environmental cues as much as possible. In some cases, microbes evolved to parasite and induce disease in the host, even being able to evade immune system surveillance (Kotwal, 1997). Either for a lack of positive interactions or an increase of infectiveness, microorganisms can induce diseases in humans, both directly as aetiological agents and indirectly by predisposing the host for the development of disease. In the case of neurodegenerative diseases, it has been described that disruption (dysbiosis) of the otherwise stable symbiotic microbial populations in the GI tract may be linked to the pathogenesis of several neuronal disorders through the bidirectional gut-brain axis (Leclair-Visonneau et al., 2020; Sundman et al., 2017; Van Den Berge et al., 2019). Hypotheses that microorganisms may infect neurons in the enteric nervous system (ENS) or produce neurotoxins that can damage the dopaminergic system and induce parkinsonism (Nunes-Costa et al., 2020) led us to revise both the potentially direct and indirect pathways by which microorganisms may induce such damage. A better knowledge about how microorganisms interact with their hosts and induce PD-like symptoms, will help understand the mechanisms underlying PD pathogenesis and enable us to design better animal models ultimately to identify new therapeutic targets (Patrick et al., 2019).

6. Gut microbiome in PD

A healthy gut microbiota in an adult human comprises some 500–1000 species of bacteria, less than 100 species of eukaryotes and only a few species of archaea (Sommer and Bäckhed, 2013; Gilbert et al., 2018). The genomic potential in this microbial ecosystem is enormous, especially if including the virome, so far the most cryptic fraction of the gut microbiome (Borrel et al., 2020; Camarillo-Guerrero et al., 2021; Gilbert et al., 2018). Such vast metabolic diversity and intricate relationships between members of the gut microbiota make it extremely difficult to identify the players, their interactions and pathways involved in processes leading to neurodegenerative diseases.

Bacteria of the phyla Bacteroidetes and Firmicutes dominate the human gut microbiome although their relative abundance is not homogeneous in different regions of GI track (Donaldson et al., 2016; Huttenhower et al., 2012; Sommer and Bäckhed, 2013). The small intestine is more acidic and oxygenated, promoting the growth of facultative anaerobes, such as members of the Lactobacillaceae and Enterobacteriaceae (Gu et al., 2013). Oxygen, host-competing nutrients and levels of different antimicrobials shape bacterial distribution gradients along the small intestine, inducing a higher bacterial density in the distal region of the small intestine, more similar to that in large intestine (Donaldson et al., 2016; Thursby and Juge, 2017). On the other hand, the large intestine environment is characterized by slow transit of faecal content, low concentrations of antimicrobials, and by the presence of more complex carbohydrates that are not absorbed in the small intestine as the main nutrient sources for the microbiota. This favours the growth of fermentative anaerobes such as those of the Bacteroidaceae and Clostridaceae in humans, and Lachnospiraceae, Bacteroideceae, Prevotellaceae and Rikinellaceae in mice (Gu et al., 2013; Johansson et al., 2008; Nava et al., 2011). The bacteria in the large intestine are differently distributed between colonic mucus layers (outer and inner) (Johansson et al., 2013). Mucin-degrading bacteria of the genera *Bacteroides* and *Akkermansia* are among the main colonizers of mucosal surfaces and tightly attached to the epithelium (Berry et al., 2013; Png et al., 2010). Diet is a key factor to modulate the gut ecosystem and its effects are reversible to a large extent (David et al., 2014). Nevertheless, because bacteria associated to mucosal surface have lower turnover rates, they tend to act as reservoirs in case of deterioration of microbiome homeostasis as a consequence of rapidly changing conditions in the gut lumen (Donaldson et al., 2016). However, a persistent harmful event like inflammation or dysbiosis can induce mucus dysfunction also affecting these microbial reservoirs (Johansson et al., 2014; Stange and Schroeder, 2019). Most microbiota studies in PD patients were performed in a single time point, however and as mentioned above, microbiota can change rapidly at different occasions, which deprives single observations of the desired significance. The gut-dominant Bacteroidetes and Firmicutes have been frequently analysed in concomitance with members of other less abundant phyla, such as Actinobacteria, Proteobacteria, Verrucomicrobia, Fusobacteria and Cyanobacteria. Despite some controversial results, massive microbiota genomic sequencing data seem to associate a lower heterogenicity and an abnormal distribution of these populations in PD patients. One longitudinal study carried out with PD patients and healthy controls for 2 years found and increase in the relative abundance of members of the Firmicutes and a decrease in members of the genus

Prevotella when compared to controls, differences that were higher in patients with faster disease progression (Aho et al., 2019). Several other studies also reported lower relative levels of *Prevotella* spp. in PD patients (Bedarf et al., 2017; Hasegawa et al., 2015; Lin et al., 2019; Scheperjans et al., 2015; Unger et al., 2016). The presence of *Prevotella* spp. in the gut has been associated with dietary fruits and vegetables consumption (Falony et al., 2016) while *Bacteroides* spp. has been associated to high-fat and protein-rich diets (David et al., 2014). It was also demonstrated that *Prevotella* spp. are involved in mucin synthesis and short-chain fatty acid (SCFA) production (Caputi and Giron, 2018), which may suggest that the lack of *Prevotella* spp. is likely associated with reduced mucin synthesis and increased gut permeability (Forsyth et al., 2011; Lin et al., 2019). However, the abundance of this taxon has been associated with gut inflammation (Iljazovic et al., 2020; Su et al., 2018). Functional interpretation based on the abundance of a single microbial group has poor relevance in the context of a polymicrobial consortium in which other members of the microbiota should be considered. Further studies are thus necessary to elucidate the apparently conflicting role of *Prevotella* spp. in PD and in other disorders (Lin et al., 2019). Other studies showed that some Lactobacillaceae and Lachnospiraceae seem also to be associated to the PD phenotype, namely that the relative abundance of the former is significantly increased while the latter are detected at lower levels in PD patients' stools (Pietrucci et al., 2019). It may be possible that the Lachnospiraceae protection factor may reside in its ability to produce SCFA namely butyrate, which has been shown to be beneficial for the maintenance of intestinal barrier integrity (Zhang et al., 2019). Integration of these data with the apparently higher relative levels of members of the Christensenellaceae also appear to confer PD patients with a poor clinical prognosis with worse cognitive impairment and pronounced gait disturbance (Barichella et al., 2019).

Epidemiological studies suggested that PD patients may consume up to 2.3-fold more milk than controls (Park et al., 2005) and that the progressive loss of SN neurons could be somehow correlated with milk intake (Abbott et al., 2016). Indeed, several gut microbiome surveys have detected higher levels of *Lactobacillus* and of *Bifidobacterium* strains in the stools of PD patients. Although these taxa are enriched in fermented milk and dairy products, the industrial strains used for fermentation represent less than 1% of the vast diversity in the *Lactobacillus* (over 500 species) and in the *Bifidobacterium* (over 100 species) genera (Parte et al., 2020) and are certainly not those detected in the human PD gut, often at higher relative abundance compared to healthy controls. Lactobacilli and bifidobacteria have been extensively used as probiotics due to their beneficial properties in maintaining intestinal barrier integrity, regulating the immune system and controlling overgrowth of pathogenic bacteria among other functions (Bottacini et al., 2017; Caputi and Giron, 2018; Derrien and van Hylckama Vlieg, 2015). These beneficial effects can bypass the gut and extend to the CNS through the microbiota-gut-brain-axis (Sun et al., 2018a, 2018b; Wallace and Milev, 2017). In animal models of gut inflammation, chronic administration of *L. rhamnosus, L. casei* and *L. mucosae* also showed CNS beneficial effects (Bravo et al., 2011; Dodiya et al., 2020; Kim et al., 2020; Xu et al., 2020). Another correlational study in PD patients revealed that erosion of *Bifidobacterium* spp. and *Bacteroides fragilis* was associated with worse Unified Parkinson's Disease Rating Scale (UPDRS) scores (Minato et al., 2017). However, some human case-control studies reported increased levels of *Lactobacillus*, *Bifidobacterium*, Verrucomicrobiaceae and *Akkermansia* in PD (Gerhardt and Mohajeri, 2018; Hill-Burns et al., 2017). So, attempts to correlate the consumption of milk or of dairy products with an increased risk of developing PD should be supported by functional studies and a more likely explanation for the hypothetical association between milk intake and PD may be the contamination of milk with organochlorine pesticides (Abbott et al., 2016). Other studies also reported an increase in the levels of Porphyromonadaceae and Rikenellaceae (both Bacteroidetes) and Turicibacteraceae (Firmicutes), and decreased levels of *Blautia* strains (Lachnospiraceae family) and of *Ruminococcus* (Firmicutes) (Jin et al., 2019; Ren et al., 2020; Wang et al., 2019).

Some species of the phylum Proteobacteria have been described as triggers of idiopathic PD. This phylum is considered the largest in the Bacteria domain for their biased association with disease. These include for example pathogenic species such as *Brucella melitensis* and *Rickettsia rickettsii*, *Bordetella pertussis, Neisseria meningitidis*, *Escherichia coli*, *Shigella dysenteriae*, *Salmonella typhi*, *Yersinia pestis* and *Helicobacter pylori* (Rizzatti et al., 2017). Interestingly, many of these bacteria belong to lineages close to the lineage from which mitochondria evolved (endosymbiotic theory by Lynn Margulis).

There are a few studies that correlated *Brucella* infection with PD and described that patients with neurobrucellosis can manifest exceptional neurological Parkinsonism-like symptoms (Jin et al., 2013; Molins et al., 1987). Concerning *Rickettsia* spp. infection, the literature is scarce with some case-reports stating that patients with scrub typhus showed parkinsonism symptoms (Kularatne et al., 2012; Premaratna et al., 2015). One of the most common members in this group of Gram-negative bacteria is probably *Escherichia coli,* the typical microbe used as an example of commensal microbiota with endotoxin (Lipopolysaccharides, LPS) in their outer membrane (Rosenfeld and Shai, 2006). Although there are many other sources of LPS namely *Salmonella typhimurium*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, the *E. coli* LPS has been used in numerous inflammatory studies including neuroinflammatory models of PD (Herrera et al., 2000; Márquez et al., 2020; Muñoz et al., 2019). However, the association of *E. coli* pathogenic strains (enteropathogenic, enterotoxigenic enteroaggregative, enteroinvasive) to the aetiology and progression of PD is still controversial. Curiously, recent studies reported that *E. coli* could help prevent amyloid aggregation (Evans et al., 2015). It should be noted that most studies in gut dysbiotic mouse models of PD have been carried out with *Citrobacter rodentium*, which is considered the rodent equivalent to a human enteropathogenic *Escherichia coli* (Schauer et al., 1995). *Citrobacter rodentium* is able to increase the oxygen supply to the gut epithelium thus triggering an unbalance between aerobes and anaerobes while promoting the expansion of mucosal-associated commensal Enterobacteriaceae (LPS-producing) and erosion of obligate anaerobes (Collins et al., 2014; Desai et al., 2016; Mullineaux-Sanders et al., 2019). This mechanism is a possible hypothesis on how bacterial infection could trigger mitochondrial antigen presentation (MitAP) and induce mitochondria-specific autoimmune response that could ultimately lead to PD (Matheoud et al., 2019, 2016). Another member of the Enterobacteriaceae associated to PD-related pathology is *Proteus mirabilis* a gut pathobiont recognized clinically as a cause of urinary tract infections and periodontitis (Dzutsev and Trinchieri, 2015). Experimental mice infection with *P. mirabilis* showed dopaminergic neuronal death, neuroinflammation and Asyn aggregation in the brain (Choi et al., 2018).

Metagenomic studies have also recently revealed a correlation between *Helicobacter pylori* infection and PD (Dardiotis et al., 2018; Wang et al., 2020), suggesting a possible involvement in PD pathophysiology (Dardiotis et al., 2018). *Helicobacter pylori* prevalence in PD patients is 3–5 fold higher than in healthy controls (Çamcı and Oğuz, 2016). Moreover, L-DOPA efficacy in PD patients is altered by the presence of *Helicobacter pylori*, a bacterium that induces gastric alterations and affects L-DOPA absorption (Pierantozzi et al., 2001), which causes a poor response and motor fluctuation in those patients (Çamcı and Oğuz, 2016; McGee et al., 2018; Mridula et al., 2017). In fact, *Helicobacter* eradication therapy improved L-DOPA treatment outcomes in PD patients (Dardiotis et al., 2018; Liu et al., 2017a, 2017b; Mridula et al., 2017). Several pathophysiological mechanisms of dopaminergic degeneration, including neurotoxin release, gut microbiome disruption and neuroinflammation mediated by the gut-brain axis, have been proposed (Dobbs et al., 2016; McGee et al., 2018). Some of the virulence factors of *Helicobacter pylori* could be involved in these mechanisms (Foo et al., 2010; Harrer et al., 2017; Jain et al., 2011; Sgouras et al., 2019), including vacuolating cytotoxin A (VacA), high temperature

requirement A (HtrA) and cytotoxin-associated gene A (CagA), which can induce direct cell damage, intestinal barrier disruption, inflammation and immune evasion (Sgouras et al., 2019). VacA has been described as an apoptotic inducer involved in mitochondrial disfunction mechanisms such as fragmentation through the activation of dynamin-related protein 1 (Drp1) (Foo et al., 2010; Jain et al., 2011), transient increase of mitochondrial translocases and accumulation of the mitochondrial DNA replication (Chatre et al., 2017) and in the translocation of cytoplasmatic Bax to mitochondria followed by cytochrome C release to cytoplasm (Kim et al., 2015). HtrA and CagA participate in intestinal barrier disruption by inducing cleavage of E-cadherin, ZO-1 and Claudin-2, while promoting bacterial transmigration and delivery of proinflammatory cytokines (Amieva et al., 2003; Harrer et al., 2017; Lapointe et al., 2010; Song et al., 2013). However, it remains unknown how these mechanisms affect dopaminergic neurons. Further studies are thus mandatory to elucidate whether the *H. pylori* virulence factors can directly or indirectly affect nigrostriatal pathways.

7. Microbial modulation of the gut-brain axis

An important bidirectional interaction between the gut and the brain exists and this communication is critical for essential physiological processes such as immune system development (Donaldson et al., 2016; Rooks and Garrett, 2016), emotional and cognitive behaviour (Carabotti et al., 2015) and to shape the composition of the gut microbiota (Donaldson et al., 2016). Increasing evidence highlights the active role of the microbiome in the modulation of the gut-brain axis through the ENS, immune system, hormones, growth factors and microbial metabolites (Carabotti et al., 2015). Alterations in this network can induce different pathologies both in the gut and in the brain (Mayer et al., 2015). However, for most of these pathologies the aetiology remains unknown. In recent years, much attention has been given to the large network of 200–600 million neurons distributed along the route linking the ENS to the CNS namely by the vagus and pelvic nerves as well as sympathetic pathways (Furness et al., 2014). In PD, recent reports argue that Asyn can spread from the gut into the brain (bottom-up effects) and vice versa (top-down effects) using the vagus network as motorway (Arotcarena et al., 2020; Forsythe and Kunze, 2013; Leclair-Visonneau et al., 2020; Mayer et al., 2015; Van Den Berge et al., 2019). Due to the bidirectional gut-brain communication one might consider two different origins for PD (brain first versus body first) (Borghammer and Van Den Berge, 2019). Indeed, recent evidence show that there are at least two different phenotypes associated to the progression of PD symptoms, one of which begins in the CNS (brain-first phenotype) and is characterized by a dopaminergic loss preceding the damage of the autonomic peripheral nervous system and the other originates in the gut with concomitant spread to the brain, in agreement with the Braak staging scheme (body-first phenotype) (Braak et al., 2003a; Borghammer, 2018; Horsager et al., 2020; Van Den Berge et al., 2019). However, these findings are not without controversy since most have failed to demonstrate Asyn propagation from the gut to the brain and also the absence of enteric Asyn pathologies in some LBD patients (Adler and Beach, 2016; Borghammer and Van Den Berge, 2019; Dorsey et al., 2018; Manfredsson et al., 2018; Uemura et al., 2018). Considering the likely multifactorial nature of PD (Johnson et al., 2019), synucleopathy models do not fully agree with clinical observations (Adler and Beach, 2016; Dorsey et al., 2018). Further progresses on how microbiota is involved in Asyn misfolding should soon enlighten the mechanism underlying Asyn aggregation and spreading.

7.1. Gut microbiome potentiates Asyn misfolding and induces prion-like PD

Asyn aggregation into LBs has been used to assess PD progression although recent findings highlighted its possible role as the trigger of the pathology. Braak and colleagues established a PD progression scheme related with the presence of LBs in the organism, suggesting that the aetiology of PD could start in the gut and/or olfactory bulb (dual-hit hypothesis), later spreading to the brain by two routes: the GI tract and the nasal epithelium (Braak et al., 2003b; Hawkes et al., 2007). The same authors suggested later that a pathogen could be the trigger of the LB expansion pattern (Braak et al., 2003a; Hawkes et al., 2009, 2007). Many recent studies supported Braak's hypothesis, by showing that Asyn aggregates spread from the ENS to CNS in a retrograde manner via the vagus nerve and corresponding branches (Kim et al., 2019; Koprich et al., 2017; Van Den Berge et al., 2019). Although this theory is generally accepted it is not exempt for criticism, starting by the Braak's study itself, wherein the attempt of establishing staging scales of Asyn dissemination in *post-mortem* PD brains sometimes failed to match clinical severity score of PD (Burke et al., 2008; Walsh and Selkoe, 2016). Also, by excluding patients with LB pathology in higher brain regions but not in the DMV (Kalaitzakis et al., 2008; Rietdijk et al., 2017), a subset of PD patients was not included. *Post-mortem* analyses have revealed that around 45 % patients with LB pathology in the SN were diagnosed with dementia, but nigral neuronal density was not associated with Braak staging or cortical LB density (Parkkinen et al., 2011). Additionally, and as mentioned before, recent studies suggest dopaminergic loss could precede Asyn spreading (Horsager et al., 2020; Milber et al., 2012). On the other hand, aged individuals without neurological symptoms had synucleinopathy matching Braak's stages 4–6 (Burke et al., 2008). Some studies reported no differences in Asyn accumulation between the gut of PD and healthy controls (Antunes et al., 2016; Gray et al., 2014; Visanji et al., 2015). Also, Asyn expression in the GI tract from PD patients (collected *post-mortem* and *ante-mortem*) was quite variable with only a few exceptions (Adler and Beach, 2016; Atik et al., 2016). Regarding animal studies with transgenic mice overexpressing human Asyn, it is noteworthy that they not always showed mesencephalic neurodegeneration (Koprich et al., 2017). Nonetheless, there are many *in vitro*, *in vivo* and clinical studies favouring Braak's hypotheses (Rietdijk et al., 2017), especially by authors that support the hypothesis that sPD starts as prion-like disease in the gut (Jucker and Walker, 2013; Kim et al., 2019; Visanji et al., 2013). This approach fits into Braak's hypothesis since it demonstrates a plausible cell-to-cell prion-like transmission of Asyn from the gut to the brain (Ayers et al., 2017; Breid et al., 2016; Steiner et al., 2018). Remarkably, oral and intravenous injection of mice with pre-formed Asyn fibrils (PFF) induced Asyn spreading by different routes (Lohmann et al., 2019). Moreover, truncal vagotomy performed in mice using a model of gastric inoculation of PFF but also in humans unresponsive to peptic ulcer affliction, significantly decreased the risk of developing PD (Svensson et al., 2015; Uemura et al., 2018). However, the prion-like transmission hypothesis is still controversial, either because Asyn spreading does not follow the characteristics of typical prionic diseases, or because there is no evidence of Asyn in the blood of PD patients, assuming that prions can be transmitted orally or through the bloodstream (Hill et al., 1997; Urwin et al., 2016). Indeed, evidence that Asyn or other human prionic diseases such as kuru, CJD or its variant can be transmitted between humans is still missing (Tamgüney and Korczyn, 2018).

Although Braak's staging scales cannot be used to prove or disprove the Asyn spreading hypothesis (Walsh and Selkoe, 2016), it is worth explaining dopaminergic degeneration and Asyn aggregates distribution as observed in Asyn PFF mouse models (Kim et al., 2019; Koprich et al., 2017; Van Den Berge et al., 2019). The unifying factor behind these controversies could lie, once again, in a key role of the gut microbiota in promoting aggregation and spreading of Asyn. Indeed, it has been described that gut microbiota can modulate Asyn expression/aggregation in the ENS (Fitzgerald et al., 2019; Sampson et al., 2016). Colonization of Asyn-overexpressing mice with PD patients gut microbiota enhanced motor deficits compared to microbiota transplants from healthy donors (Sampson et al., 2016). Gut microbiota can modify Asyn aggregation through different but not fully understood mechanisms. For

example, some studies suggest that LPS, a key component of the outer membrane of Gram-negative bacteria, can accelerate Asyn aggregation *in vitro* (Bhattacharyya et al., 2019; Kim et al., 2016) or even aggravate motor impairment symptoms in an Asyn-overexpressing mouse model (Gorecki et al., 2019). Some bacteria, such as some members of the Enterobacteriaceae, can synthesize functional amyloid proteins in a soluble form that later aggregate extracellularly to help form biofilms (Curli fibers) and assist surface attachment (Tursi and Tükel, 2018). The assembly of the Curli protein (CsgA) is guided by other Curli specific genes (Csg) namely CsgC and CsgE that are able to interact with Asyn and induce or inhibit its aggregation (Chorell et al., 2015; Evans et al., 2015). CsgA must then be released extracellularly to avoid intracellular aggregation that would otherwise damage bacterial metabolism. Therefore, to prevent aggregation, CsgA is inhibited by CsgC at sub-stoichiometric concentrations (Evans et al., 2015). Interestingly, although CsgC can inhibit aggregation, the related CsgE can promote Asyn aggregation *in vitro* (Chorell et al., 2015; Evans et al., 2015). The ability of bacterial proteins to potentiate Asyn aggregation has also been observed *in vitro* with a functional amyloid FapC from *Pseudomonas aeruginosa* (Proteobacteria) (Christensen et al., 2019). The effect of these bacterial amyloid proteins goes beyond *in vitro* studies since oral administration of curli-synthetizing bacteria in aged rats and nematodes were also confirmed to concomitantly increase the production and aggregation of Asyn (Chen et al., 2016). Asyn-overexpressing mice mono-colonized with Curli-synthetizing *E. coli* showed GI dysfunction with Asyn aggregation, both in the gut and in the brain, associated to motor impairment (Sampson et al., 2020). It is well known that the levels of Enterobacteriaceae associated to gut mucosa are more pronounced in PD compared to healthy controls and that their presence correlate positively with worse clinical outcomes (Forsyth et al., 2011; Scheperjans et al., 2015). Intra-intestinal injection of Curli CsgA also promoted induction of Asyn aggregation (Sampson et al., 2020). These authors suggest that extracellular Asyn could act as an antimicrobial agent and in that sense modulate the PD gut microbiome (Sampson et al., 2016), an hypothesis already put forward by different authors for other amyloid proteins (Kumar et al., 2016). However, this effect was proposed to be reversible in a promising study using Asyn-overexpressing *C. elegans* model in which the administration of probiotic *Bacillus subtilis* inhibited and even reversed Asyn aggregation (Goya et al., 2020). These studies open the possibility to innovative bacteriotherapies based on probiotics with anti-Asyn aggregation properties. Bacterial short-chain fatty acids (SCFAs) can also modulate Asyn aggregation mediated by immune system responses. In a recent study, germ-free Asyn-overexpressing mice transplanted with faecal material from PD patients showed motor impairments, higher abundance of *Proteus* spp., *Bilophila* spp., and *Roseburia* spp. and erosion of Lachnospiraceae, Rikenellaceae, Peptostreptococcaceae and *Butyricicoccus* spp., collectivelly leading to a significantly altered SCFA profile that promoted Asyn-reactive microglia in the brain. These effects were not observed in mice transplanted with faecal material from healthy donors nor in non-susceptible mice, which reveals that the combination of genetic and environmental factors is likely necessary for disease development (Sampson et al., 2016).

7.2. Gut microbiome induces gut and brain inflammation leading to immune-like PD

The intestinal barrier is the first natural barrier and the longest surface of our body (260−300 m^2) exposed to the external environment (Helander and Fändriks, 2014). It also contains around $3.8{\cdot}10^{13}$ microbial cells (Sender et al., 2016). The loss of intestinal barrier integrity is associated with different diseases, namely diabetes (Sorini et al., 2019), infection (Baba et al., 2009) and also PD (Matheoud et al., 2019; Perez-Pardo et al., 2019). The maintenance of this barrier is synergistically coordinated by the immune system and by the gut microbiota and such beneficial interaction is of utmost importance for both the immune system development (Donaldson et al., 2016; Rooks and Garrett, 2016) and for the modulation of the composition of the microbiota determined to certain extent by nutrient availability, content transit rate and immune system activity (Donaldson et al., 2016). An unbalanced gut microbiota or immune system decay can lead to gut dysbiosis, inducing an inflammatory response with partial translocation of the intestinal content to the bloodstream and inevitably to distant parts of the body (Engen et al., 2017; Houser and Tansey, 2017; Matheoud et al., 2019). Nonetheless, the CNS is protected by the blood brain barrier (BBB) a true barrier and a crucial mediator of CNS homeostasis that separates the blood from the neuronal parenchyma and which isolates the brain from harmful molecules. This BBB however can be compromised in PD as a consequence of gut dysbiosis, creating a self-amplified loop leading to activation and recruitment of peripheral immune cells and neurodegeneration (Gray and Woulfe, 2015; Campos-Acuña et al., 2019; Peralta Ramos et al., 2019; Sweeney et al., 2018).

Faecal and mucosa-associated gut microbiota also differ between individuals with PD and healthy controls (Unger et al., 2016). PD patients exhibit intestinal inflammation (Devos et al., 2013) and it has been described that the infiltration of monocytes and T-cells in the brain parenchyma is initially elicited by the microbiome associated to the gut mucosa (Campos-Acuña et al., 2019; Peralta Ramos et al., 2019). These cells appear to be essential to drive both local brain inflammatory responses as well as the engagement of peripheral immune mechanisms (Harms et al., 2018). In addition, intestinal infection stimulates mitochondrial antigen presentation and autoimmune mechanisms that drive cytotoxic mitochondria-specific $CD8^+$ T cells to the periphery and to the brain (Matheoud et al., 2019, 2016). This again suggests that mitochondria retained the capacity to activate neuronal innate immunity (Cardoso and Empadinhas, 2018; Matheoud et al., 2019). There are also evidences that PD may be a consequence of combined effects between inflammation and Asyn vagal spreading (Campos-Acuña et al., 2019; Johnson et al., 2019), being gut dysbiosis the common trigger (Johnson et al., 2019). Other studies suggest that an increment of gut-microbiota immunoreactivity to IgA can induce a gut proinflammatory phenotype. IgA is the most abundant antibody produced in mouse and human and it can bind to specific microbiota controlling their colonization levels and defining subsets of population growth (Pabst and Slack, 2020). Recent studies have shown specific gut-microbiota immunoreactivity to IgA-positive plasma cells circulating in the peripheral blood (Mei et al., 2009) and holding the ability to migrate to other organs (Shalapour et al., 2017) and influence autoimmune responses (Bashford-Rogers et al., 2019). IgA-coated microbiota have been considered a marker for proinflammatory gut microbiota (Pröbstel et al., 2020). Some bacteria contain immunoreactive motifs that are potent IgA inducers as observed in Multiple Sclerosis and Inflammatory Bowel Disease (Palm et al., 2014; Pröbstel et al., 2020). This highlights the role of the gut microbiota as main players in the dynamic migration of plasma cells between the gut and the brain (Fitzpatrick et al., 2020; Pröbstel et al., 2020; Shalapour et al., 2017). However, it is interesting to question the reasons why immunostimulatory bacteria in the gut may lead to the recruitment of regulatory immune cells to the CNS (Pröbstel et al., 2020; Rojas et al., 2019). A plausible explanation could be that a breached intestinal barrier may allow gut microbiota–specific immune cells to act as systemic mediators able to penetrate the CNS during acute neuroinflammation (Buscarinu et al., 2016; Pröbstel et al., 2020). Recent reports show that gut-educated IgA plasma cells are present in meningeal venous sinuses of slow blood flow whose fenestrations can potentially allow access of blood-borne pathogens into the brain (Fitzpatrick et al., 2020).

7.3. Gut microbiota-derived metabolites

7.3.1. Short-chain fatty acids (SCFAs)

SCFAs are the products of dietary indigestible polysaccharide fibres after fermentation by some members of the gut microbiota. SCFAs are carboxylic acids with a chain of 2–6 carbons namely acetate, propionate

and butyrate, the latter being the more abundant. SCFAs act at different levels, especially in the maintenance of intestinal barrier integrity and have an anti-inflammatory effects in the gut (Lewis et al., 2010). However, their properties go beyond the boundaries of the GI tract, also having important effects in the immune system, microglia and neurons, and consequently important players in PD (Dalile et al., 2019; De Vadder et al., 2014; Lewis et al., 2010; Parada Venegas et al., 2019). Indeed, butyrate has shown protective effects against Asyn aggregation. Moreover, butyrate has been described to activate the autophagic Atg5-dependent PI3k/Akt/mTOR pathway increasing Asyn degradation (Qiao et al., 2020) or to indirectly rescue dopaminergic cells from Asyn-induced transcriptional deregulation (Paiva et al., 2017) or even to mediate the stimulation of glucagon-like peptide-1 (Liu et al., 2017a, 2017b). Butyrate has been shown to promote the synthesis of catecholamines by inducing the transcription of tyrosine hydroxylase gene (Nankova et al., 2014). Human studies confirmed that faecal SCFAs concentrations were significantly reduced in PD patients compared to controls and that this was associated with low abundance of SCFAs-producing bacteria namely *Bacteroides* spp. and Prevotellaceae (Unger et al., 2016). However, controlled animal studies did not confirm these observations (Mulak, 2018). Animals colonized with PD donor-derived microbiota showed higher levels of faecal propionate and butyrate inducing Asyn reactive microglia (Sampson et al., 2016). On the other hand, the plasma from PD patients contained elevated levels of SCFAs and this was correlated with disease severity (Shin et al., 2020). Considering that the proportion of different SCFAs is an important factor and that SCFAs have different properties, one would expect that different combinations would have differential impact. In this context, acetate and butyrate, but not propionate, have been shown to stimulate mucin secretion in the rat colon (Barcelo et al., 2000) while butyrate activated MUC2 gene expression in the mouse colon (Gaudier et al., 2009). However, daily administration of butyrate enemas did not affect MUC2 expression in human colonic biopsies (Scheppach et al., 1992). Another element to be considered is the type of SCFAs-producing bacteria. Although the studies in PD patients are difficult to interpret due to high variability between samples, the levels of SCFAs-producing bacteria such as *Prevotella*, Lachnospiraceae, Verrucomicrobiacea, *Akkermansia*, Lactobacillaceae and Bifidobacteriacea were often altered in PD patients. Most studies showed that the relative abundance of *Prevotellla* spp. and Lachnospiraceae were decreased while those of Verrucomicrobiacea, *Akkermansia* spp., *Lacatobacillus* spp. and Bifidobacteriaceae were frequently increased (Bedarf et al., 2017; Heintz-Buschart et al., 2018; Keshavarzian et al., 2015; Petrov et al., 2017; Scheperjans et al., 2015; Unger et al., 2016). It is hard to determine which bacterial combination will result in higher levels of SCFAs and additional studies will be needed to further clarify some of the contradictory findings obtained from human subjects, and also to unravel the role of gut microbiota-derived SCFAs or of their imbalance in the mechanisms leading to or protecting from PD.

7.3.2. Other metabolites

Other important metabolites produced by the gut microbiota have recently caught scientists' attention because of their participation in the neurodegenerative process. For example, the metabolic activity of some gut microbes releases gases with signalling properties (gasotransmitter), namely hydrogen sulphide (H_2S) and hydrogen gas (H_2), which can be found in the plasma and in the gut where they may have neuroprotective properties (Cakmak, 2015; Shen et al., 2013; Wang, 2003). In murine models of neurotoxicity-induced PD, H_2S breathing treatment prevented dopaminergic loss, microglia activation and movement deficits (Hu et al., 2010; Kida et al., 2011). Members of the genus *Prevotella* have been described to be involved in H_2S production, and as mentioned above, their abundance is underrepresented in PD patients gut microbiota (Gerhardt and Mohajeri, 2018; Scheperjans et al., 2015; van Kessel and El Aidy, 2019). The hydrogen gas (H_2) produced by some *Clostridium* spp. and *Blautia* spp. was also suggested to have anti-radical and anti-inflammatory properties (Ostojic, 2018). Animals treated with H_2-enriched drinking water showed dopaminergic protection and motor improvement in the neurotoxicity-induced murine model of PD (Fu et al., 2009; Fujita et al., 2009). Interestingly, some authors also reported a correlation between the lack of *Blautia coccoides* and *Clostridium leptum* and neurodegeneration in PD patients due to a decrease in H_2 availability for neuroprotection (Suzuki et al., 2018; van Kessel and El Aidy, 2019).

Some lactate-derivative metabolites found to be increased in the serum of both idiopathic and Parkin-mutated PD patients could be related with the genus *Clostridium* (Hatano et al., 2016; Okuzumi et al., 2019). Moreover, p-cresol sulphate released by some *Clostridium* spp. and Bacteroidetes (Saito et al., 2018) was also found to be increased in the CSF of PD patients (Willkommen et al., 2018), although it was not detected in blood samples (Hatano et al., 2016; Okuzumi et al., 2019).

An important issue to discuss related with the progression and treatment of PD is the ability of some bacteria to participate actively in the metabolism and in the degradation of catechol group and diverse catecholamines. For example, *Ralstonia pickettii* (formerly *Pseudomonas pickettii*) that seems to be associated with a pro-inflammatory gut, was found at increased relative levels in PD patients gut microbiota (Engen et al., 2017; Gerhardt and Mohajeri, 2018; Scheperjans et al., 2015), and is able to degrade the catechol group reported to be decreased in PD patients (Burté et al., 2017; Okuzumi et al., 2019). This catechol catabolism includes the benzoate degradation pathway that can lead to adrenergic stress and increase bacterial virulence (Rooks et al., 2014). Some bacteria of the *Lactobacillus* and *Enterococcus* genera are able to metabolize catecholamines including dopamine because they express tyrosine decarboxylase (Perez et al., 2015; Zhu et al., 2016). Indeed, the relative abundance of *Lacotobacillus* spp. was found to be increased in PD guts (Barichella et al., 2019; Pietrucci et al., 2019; van Kessel et al., 2019). This can have a tremendous impact during L-DOPA treatment, compromising the levels of dopamine that effectively reach the brain (van Kessel et al., 2019). The co-prescription of human tyrosine decarboxylase inhibitors such as Carbidopa does not seem to inhibit bacterial tyrosine decarboxylase, but stimulates an increase in luminal levels of dopamine and tyrosine decarboxylase-producing bacteria (van Kessel et al., 2019; van Kessel and El Aidy, 2019). This is in accordance with the abnormal increase in dopamine levels not related with L-DOPA dosage as those found in the serum of PD patients as a result of bacteria and human levodopa metabolism (Kustrimovic et al., 2016; Rajda et al., 2005). High levels of dopamine in the blood may have detrimental effects to the immune system (Pinoli et al., 2017; Sarkar et al., 2010), which is critical to keep the complex balance between immune neuroprotection and neuroinflammation (Doty et al., 2015).

A recent metabolome analysis of faecal samples from PD patients revealed other metabolites that may be related to the disease (Vascellari et al., 2020). It has been observed that cadaverine, ethanolamine, hydroxypropionic acid, isoleucine and leucine, phenylalanine, and thymine were increased. On the other hand, linoleic acid, oleic acid, nicotinic acid (vitamin B3), glutamic acid, pantothenic acid (vitamin B5), pyroglutamic acid, succinic acid, and sebacic acid were significantly decreased. The authors correlated the levels of these metabolites with the presence or the absence of some bacterial genera. Positive correlations were found between vitamin B3 and vitamin B5 and the abundance of the genera *Lachnospira*, *Pseudobutyrivibrio* and *Roseburia*. However, the abundance of *Serratia* showed a negative correlation with vitamin B3 as was the abundance of *Bifidobacterium* in relation to vitamin B5 (Vascellari et al., 2020). Dysfunction in the metabolism of B3 and B5 vitamins and in their bioavailability may induce energy metabolism alterations, which has been proposed to be associated with several neurodegenerative disorders (Fricker et al., 2018; Patassini et al., 2019; Yoshii et al., 2019). In fact, chronic vitamin B3 deficits have long been described as a characteristic of PD patients (Bender et al., 1979; Wakade et al., 2014).

Cadaverine is an additional metabolite produced by bacteria and

involved in human metabolism (Kovács et al., 2019). The level of this diamine is positively correlated with the presence of Streptococcaceae but negatively correlated with members of the family Sphingobacteriaceae (de las Rivas et al., 2006; Vascellari et al., 2020). Cadaverine, as other polyamines such as putrescine and spermidine showing toxic effects in mice (Santoru et al., 2017), have been found to be increased in PD patients and proposed to be involved in the formation of LBs (Makletsova et al., 2019). Moreover, cadaverine inhibits intestinal transit in PD mouse models contributing to the promotion of a proinflammatory environment and motility dysfunctions of the GI tract (Sánchez et al., 2017; van Kessel and El Aidy, 2019).

Also the levels of linolenic acid have been found to be lower in PD patients (Schulte et al., 2016; Vascellari et al., 2020). This decrease may be negatively correlated with the presence of members of the Bifidobacteriaceae and Bacteroidaceae (Vascellari et al., 2020). Linolenic acid is well-known by its antioxidant properties and its decrease may contribute to an excess of oxidative stress in PD patients (Hernando et al., 2019), which together with the decrease of antioxidant vitamins namely B3 and B5, could contribute to increment the proinflammatory and prooxidant environment that likely promotes some of the mechanisms underlying neurodegeneration (Moretti and Peinkhofer, 2019).

Aminoacidic metabolism can also be modulated by the gut microbiota (Trupp et al., 2014). An increment of isoleucine, leucine and phenylalanine has been observed in the plasma of PD patients (Vascellari et al., 2020; Zhao et al., 2018) and associated to the presence of aminoacid-fermenting gut bacteria (Macfarlane et al., 1988). Intriguingly, a few bacteria and some eukaryotic microbes are also able to synthesize non-proteinogenic aminoacids such as β-*N*-methylamino--L-alanine (BMAA), which has been proposed to be misincorporated into proteins and potentially lead to a loss of function and/or misfolding (Nunes-Costa et al., 2020; Dunlop et al., 2013; Bullwinkle et al., 2014; Dunlop and Guillemin, 2019). Consequently, microbially-produced BMAA could hypothetically be involved in the aetiology of neurodegenerative disorders such as PD (Karlsson et al., 2009; Nunes-Costa et al., 2020). Interestingly, BMAA has been detected in the CNS (Berntzon et al., 2015) and in proteins from the brain of patients with neurodegenerative disease but not in healthy controls (Dunlop et al., 2013). Although most mechanisms underlying BMAA neurotoxicity still remain unknown, recent studies demonstrate that microbial BMAA indeed targets the mitochondria and concomitantly activates neuronal innate immunity (Silva et al., 2020).

8. Conclusions

We have witnessed important advances in the last few years, which augurs well for future new strategies to combat the current pandemic of Parkinson's Disease. Although we still do not know the aetiology of idiopathic PD nor have a therapy to arrest the associated neurodegenerative process, the many exciting advances in PD research allow us to propose a unifying theory that includes some of the multiple aspects that probably lead up to the characteristic manifestation of the disease. The coexistence of different types of parkinsonism are in line with the possibility of different aetiologies, leading us to agree that PD is indeed a multi-aetiological syndrome (Johnson et al., 2019). Evidence supports that the disease evolves from different triggers and that a combined series of unfortunate events in genetically susceptible individuals potentiates its progression. The most recent data clearly point to the fact that either microbial infections, bacterial or mitochondrial toxins or gut dysbiosis may independently trigger PD, and that perturbations of some essential cellular processes such as mitochondrial function may be

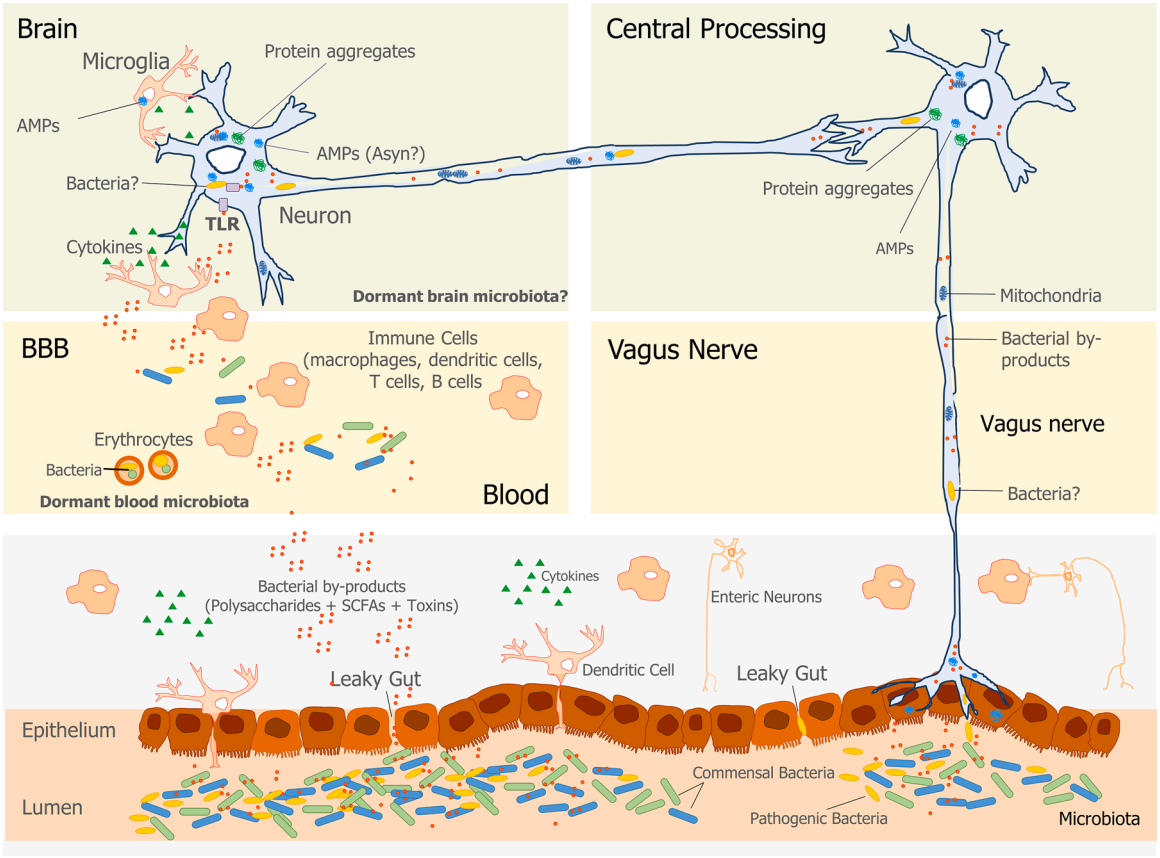

Fig. 1. Schematic diagram of PD Gut-Immune-Brain axis. Chronic sub-clinical gut dysbiosis promotes the loss of intestinal barrier integrity allowing microbial by-products to reach the brain through the vagus nerve or the blood, triggering innate immune responses such as Asyn expression, mitochondrial dysfunction, inflammation, neurodegeneration and ultimately PD.

common facilitators, and finally that the spread of Asyn aggregation produced as an antimicrobial or antimitochondrial agent of innate immunity to the brain may most likely culminate in PD neurodegeneration (Fig. 1). Our reasoning is based on the knowledge that our gut houses a large community of microbes that for millions of years shaped the evolution of our mammal and primate ancestors and later of our own evolution to the point of intimately participating in our physiological processes for better or worse, directly or indirectly, and making use of different types of messengers from simple metabolites to more intricate mediators of our immune system, making our health or disease depend on it. The bidirectional communication between the brain and the gut, critical for important physiological processes involves a large network of hundreds of million neurons distributed along the ENS that can be targets of the gut microbiota. In case the intestinal barrier that efficiently protects the inner body from external aggressions loses its integrity due to gut dysbiosis (disruption of the gut ecosystem), this will not only impact the regulation of inflammatory and immune responses at the mucosal level but also dopaminergic metabolism as well as a balanced production of protective SCFAs and of other metabolites that may be noxious. The breach will facilitate entry of microbial pathobionts into previously sterile tissues thus inducing Asyn spread and aggregation. Understanding the mechanisms underlying this convergent and sequential process will certainly help devise innovative strategies to prevent or ameliorate PD. Efforts have already been made, such as the discovery that specific bacteria can indeed inhibit Asyn aggregation, help plasma cells protect meningeal venous sinuses, as well as decrease gut inflammation induced by pathogenic microbes. Hence, a next generation research agenda in neuromicrobiology is mandatory toward a profound understanding of the molecular mechanisms of microbe-microbe and microbe-host interactions that allow microbes to elicit and sustain PD, but also to unveil new strategies to intervene as early as possible.

Author agreement

All the authors have seen and approved the final version of the manuscript being submitted. All the authors warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Author contributions

Nuno Empadinhas & Sandra M. Cardoso: Conceptualization, Writing, Reviewing and Editing and Supervision. Mario F. Munoz-Pinto: Writing, Original draft preparation, Investigation.

Funding

This work was supported by Mantero Belard Neurosciences Prize 2016 (MB-40-2016); FMUC-PEPITA (2018); European Regional Development Fund (ERDF), through the Centro 2020 Regional Operational Programme under project CENTRO-01−0145-FEDER-000012 (HealthyAging2020) and through the COMPETE 2020 - Operational Programme for Competitiveness and Internationalization and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, under projects POCI-01−0145-FEDER-030712, POCI-01–0145-FEDER-029221 (PTDC/BTM-TEC/29221/2017), PTDC/MED-NEU/3644/2020, and UIDB/04,539/2020.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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