

# Potential roles of functional bacterial amyloid proteins, bacterial biosurfactants and other putative gut microbiota products in the etiopathogeny of Parkinson's Disease

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**Abstract:** An increasing number of studies provide evidence for the existence of a microbiota-gut-brain axis and its potential involvement in the development of sporadic Parkinson's disease and other neurodegenerative conditions. The neuropathologic hallmark of Parkinson's disease is the presence of brain intraneuronal aggregates of misfolded alpha-synuclein, known as Lewy bodies. Some gut microbiota products may trigger alpha-synuclein conformational changes in the neurons of the enteric nervous system, which can then spread to the brain in a prion-like fashion through the vagus nerve. Others may interfere with neuroinflammatory pathways and susceptibility to neurodegeneration. In this review, we assess the potential role of putative gut microbiota products in the etiopathogeny of Parkinson's disease, with a special emphasis on functional bacterial amyloid proteins, bacterial biosurfactants, endotoxins and short-chain fatty acids. The possible roles of molecular hydrogen, a common by-product of bacterial fermentation, are also addressed.

## Abbreviations

<b>BBB:</b>	blood brain barrier
<b>CNS:</b>	central nervous system
<b>Fap:</b>	functional amyloid in <i>Pseudomonas</i>
<b>H-NS:</b>	histone-like nucleoid-structuring protein
<b>IHF:</b>	integration host factor
<b>IL-1<math>\beta</math>:</b>	interleukin-1 beta
<b>iNOS:</b>	inducible nitric oxide synthase
<b>LPS:</b>	lipopolysaccharide
<b>NF-<math>\kappa</math>B:</b>	nuclear factor kappa-light-chain-enhancer of activated B cells
<b>PD:</b>	Parkinson's disease
<b>SCFA:</b>	short-chain fatty acids
<b>SIBO:</b>	small intestine bacterial overgrowth
<b>TLR:</b>	toll-like receptor
<b>TNF-<math>\alpha</math>:</b>	tumour necrosis factor-alpha

## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system (CNS) resulting in progressive motor and non-motor manifestations (Berg *et al.*, 2015; Braak *et al.*, 2003). The etiopathogeny of sporadic cases is incompletely understood, and currently, there are no disease-modifying treatments.

Pathologically, PD is a proteinopathy characterized by misfolding, aggregation, and intraneuronal accumulation of alpha-synuclein, with subsequent neuroinflammatory changes and neurodegeneration (Braak *et al.*, 2003; Spillantini *et al.*, 1998; Spillantini *et al.*, 1997; Walker *et al.*, 2016). As in the case of other alpha-synucleinopathies, the misfolded alpha-synuclein gains amyloid properties and putative neurotoxic functions (Araki *et al.*, 2019; Braak and Del Tredici, 2017). Self-aggregation of the misfolded alpha-synuclein results in intraneuronal aggregates known as Lewy bodies, the pathological hallmarks of PD (Araki *et al.*, 2019; Baba *et al.*, 1998; Braak *et al.*, 2003; Spillantini *et al.*, 1998; Spillantini *et al.*, 1997; Walker *et al.*, 2016).

Based on their previous findings concerning the topographical sequence (or stages) of Lewy pathology development in the brain of people with PD and the early

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presence of Lewy bodies in the neurons of the enteric nervous system, olfactory bulb, and dorsal motor nucleus of the vagus nerve, Braak *et al.* (2006) hypothesised that the alpha-synuclein misfolding process originates in the nasal mucosa and the gut (Braak *et al.*, 2006; Braak *et al.*, 2003; Friedland, 2015; Hawkes *et al.*, 2007). This was further refined into the dual-hit theory, which states that a neurotropic infectious pathogen, viral or with prion-like properties, enters the brain by transsynaptic retrograde transmission via the vagus and olfactory nerves, thus bypassing the circulatory system and blood-brain-barrier (BBB) (Angot and Brundin, 2009; Hawkes *et al.*, 2007, 2009; Walker *et al.*, 2016). The current view is that an exogenous factor triggers the initial alpha-synuclein conformational changes, which then self-propagate mainly via the olfactory and/or vagus nerve, reaching the brain (Araki *et al.*, 2019; Braak and Del Tredici, 2017). The triggers for the pathologic amyloid transformation of alpha-synuclein remain unknown.

Arguments for the potential roles of the microbiota-gut-brain axis in the etiopathogeny of sporadic PD include the early involvement of the enteric nervous system, with chronic constipation that typically occurs before the motor onset of the disease (Berg *et al.*, 2015; Martinez-Martin *et al.*, 2007), the early presence of Lewy pathology in intestinal neurons (Braak *et al.*, 2006; Braak *et al.*, 2003) and presence of proinflammatory gut dysbiosis in people with PD, with increases in faecal *Verrucomicrobiaceae* and *Akkermansia*, which degrade the intestinal mucus layer, and decreases in the beneficial *Prevotellaceae*, *Roseburia* and *Faecalibacterium* being more consistently reported (Aho *et al.*, 2019; Baldini *et al.*, 2020; Boertien *et al.*, 2019; Cattaneo *et al.*, 2017; Cirstea *et al.*, 2020; Gabrielli *et al.*, 2011; Hill-Burns *et al.*, 2017; Keshavarzian *et al.*, 2015; Minato *et al.*, 2017; Nishiwaki *et al.*, 2020; Nuzum *et al.*, 2020; Pietrucci *et al.*, 2019; Scheperjans, 2016; Unger *et al.*, 2016). The causal relation between the microbiota changes and PD is still unclear; however, Minato *et al.* (2017) found that lower baseline fecal *Bifidobacterium* and *Atopobium* correlate with PD symptom severity at 2 years. The functional impact of these differences in the composition of the gut microbiota also needs clarification, various models predicting changes in the expression of some gut microbiota metabolites, with possible consequences on its global function (Baldini *et al.*, 2020; Bedarf *et al.*, 2017; Cirstea *et al.*, 2020; Nishiwaki *et al.*, 2020; Nuzum *et al.*, 2020). Contextual indirect evidence for the potential role of the microbiota in the etiopathogeny of PD also comes from epidemiological studies that show increased risk of PD in people with prior *Helicobacter pylori* infection (Huang *et al.*, 2018; Nielsen *et al.*, 2012) and with inflammatory bowel disease (Park *et al.*, 2019; Villumsen *et al.*, 2019; Weimers *et al.*, 2019), the latter mitigated by early effective treatment (Peter *et al.*, 2018). Furthermore, the risk of PD is lower in people that underwent truncal vagotomy for peptic or duodenal ulcer (Liu *et al.*, 2017; Svensson *et al.*, 2015), as well as in those that underwent an appendectomy and possibly tonsillectomy (Liu *et al.*, 2020), putative explanations being disruption of the pathology dissemination pathway and removal of tissues with high alpha-synuclein load, respectively. In addition, intestinal inflammatory changes and altered intestinal

barrier permeability have been reported in people with PD (Houser *et al.*, 2018; Schwierzt *et al.*, 2018), suggesting that direct contact between alpha-synuclein found in enteric neurons and microbiota products is plausible. Another study supporting the plausibility of direct contact between human alpha-synuclein and microbiota products within the gut found that enteric neurons' overexpression of alpha-synuclein can be induced by local viral infections (Stolzenberg *et al.*, 2017), while Uesaka *et al.* (2016) found that the gut lining contains a category of enteroendocrine cells having properties of neurons and being connected directly to alpha-synuclein-containing neurons (Uesaka *et al.*, 2016). Arguments supporting the role of the gut microbiota in the etiopathogeny of PD also come from experimental animal models and *in vitro* studies, the most notable being brought by Sampson *et al.* (2016), who performed *in vivo* experiments on alpha-synuclein overexpressing mice, showing that the gut microbiota is needed for Lewy body pathology, motor impairment, and microglia activation. Such data suggested an active gut-brain signalling pathway between the microbiota and the brain (Sampson *et al.*, 2016). Moreover, microglia activation, an important player in PD (Hirsch and Hunot, 2009), is modulated by gut bacteria in mice (Erny *et al.*, 2015).

Amyloids are self-aggregating proteins with fibrillary morphology and beta-sheet secondary structure. *In vitro* studies have shown that alpha-synuclein can aggregate, forming amyloid fibres or fibrils with a cross-beta structure (Conway *et al.*, 1998; Greenwald and Riek, 2010; Soto, 2003). These results are supported by *in vivo* murine experiments on the propagation of alpha-synuclein amyloid fibrils, which can spread from neuron to neuron in a prion-like fashion (Luk *et al.*, 2012; Masuda-Suzukake *et al.*, 2013). As mentioned, Lewy bodies are abnormal aggregations of misfolded alpha-synuclein encountered in PD and other alpha-synucleinopathies (Araki *et al.*, 2019; Baba *et al.*, 1998; Braak *et al.*, 2003; Spillantini *et al.*, 1998; Walker *et al.*, 2016). Thus, PD is actually a type of amyloidosis in which misfolded alpha-synuclein is the pathologic amyloid, resulting in the accumulation and spread of alpha-synuclein amyloid fibrils (Araki *et al.*, 2019), not only in the brain but also in the autonomic nerve fibres that innervate visceral organs such as the intestine and heart (Gelpi *et al.*, 2014).

Environmental factors are thought to play important roles in triggering alpha-synuclein misfolding and Lewy body formation in sporadic PD but are largely unknown. Recent evidence shows that cross-reactivity and seeding between distinct amyloid proteins and alpha-synuclein can occur (i.e., transient protein-protein interactions between distinct amyloid proteins and native alpha-synuclein can result in the formation of amyloid alpha-synuclein) (Chen *et al.*, 2016; Chorell *et al.*, 2015; Evans *et al.*, 2015; Sampson *et al.*, 2020). Considering the dual-hit hypothesis and the large surface of the gastrointestinal tract where alpha-synuclein in enteric neurons could be exposed to the endoenvironment of the intestinal lumen, molecular xenobiotics of the gut microbiota pose a particular interest as possible triggers of the initial alpha-synuclein misfolding and self-aggregation events, which may then self-propagate along the neurons of the vagus nerves and sympathetic chains, reaching the brain.

Increasingly detailed knowledge of the mechanisms by which the gut microbiota products contribute to neurodegeneration could lead to the identification of valuable therapeutic targets and the development of therapeutic interventions that could slow down, or even stop or prevent, pathological protein accumulation in the brain. The scope of this review is to highlight the main products of bacteria found in the gut microbiota that are potentially involved in the etiopathogeny of sporadic PD (see [Tab. 1](#)). Most of the existing literature reports data on short-chain fatty acids (SCFA). Relatively few data (coming mostly from animal or cellular models) are available on functional bacterial amyloid proteins, bacterial biosurfactants, endotoxins, and other categories of bacterial products. Thus, our review will provide a concise description of the possible contribution of these products to the development and spread of PD pathology. With this purpose, we will provide a critical presentation of the role of the functional bacterial amyloid proteins curli and functional amyloids in *Pseudomonas* (Fap), the bacterial biosurfactant rhamnolipid, the bacterial endotoxins lipopolysaccharides (LPS), and the microbial metabolites SCFA (also see [Fig. 1](#)). We will also discuss molecular hydrogen, a common by-product of bacterial carbohydrate metabolism with putative neuroprotective effects.

[Fig. 1](#) exemplifies the possible roles of functional bacterial amyloid proteins (Curli and Fap), bacterial biosurfactants, lipopolysaccharide (LPS) and short-chain fatty acids (SCFA), putatively produced by the gut microbiota, in the development and spread of sporadic Parkinson's disease (PD) pathology. PD is a proteinopathy characterized by amyloid transformation of native alpha-synuclein, with pathologic misfolding, aggregation and accumulation of aggregates (i.e., Lewy bodies, Lewy neurites) and subsequent neurodegeneration. The Braak hypothesis and dual-hit theory (see text) state that in most people with PD the alpha-synuclein misfolding process originates in the gut and olfactory mucosa, where it is initiated by an unknown pathogen. The current view is that alpha-synuclein conformational changes spread transsynaptically, from the gut and olfactory mucosa neurons to the brain, *via* the respective nerves, by a prion-like mechanism. In this review we focus on spreading *via* the vagus nerve, one of the main bidirectional communication pathways of the gut-brain axis. The presence of a proinflammatory and mucolytic microbiota in people with PD, as well as lower concentrations of SCFA, results in alteration of the intestinal barrier, possibly allowing direct contact between some gut lumen xenobiotics (such as the above mentioned bacterial products) and enteric neurons that express alpha-synuclein. Moreover, intestinal inflammatory changes may increase alpha-synuclein expression in enteric neurons. *In vitro* and *in vivo* (animal models) studies suggest that the functional bacterial amyloid proteins curli and Fap, the bacterial biosurfactant rhamnolipid and the endotoxin LPS are able to induce alpha-synuclein conformational changes and pathologic aggregation. Further details are found in [Tab. 1](#).

### Functional Bacterial Amyloid Proteins—Curli and Fap

Amyloids were initially described in association with human diseases, including the broad group of neurodegenerative

proteinopathies, PD included. They consist of protein monomers, which can self-assemble, forming beta-strands perpendicular to the fibril axis, the so-called cross-beta structure ([Nelson et al., 2005](#); [Tycko, 2004](#)).

The concept of functional amyloids was proposed for the first time by [Chapman et al. \(2002\)](#) who observed that curli protein produced by *Escherichia coli* is biochemically similar to amyloid proteins that are associated with diseases. Since then, functional amyloids have been identified in many organisms, including humans, being involved in a broad variety of physiological functions ([Fowler et al., 2007](#); [Hammer et al., 2008](#)). It is thought that the amyloid proteins are so widespread in physiology because their fibrillary aggregate-forming structure confers them with excellent building material properties. Although functional amyloids from different organisms have the same ability to form amyloid fibrils, their monomers share little to no similarity in amino acid sequence ([Shewmaker et al., 2011](#)).

Functional bacterial amyloid proteins are extracellular proteins produced by many symbiotic and pathogenic bacteria, including *Escherichia*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Bacillus*, *Mycobacteria*, *Citrobacter*, *Klebsiella*, and *Salmonella* species, in which they support growth and survival. They are insoluble and have high mechanical and chemical stability ([Otzen, 2010](#)). One of their main roles is related to biofilm formation, an extracellular matrix with a complex structure that provides a living environment for most gut bacteria ([O'toole et al., 2000](#)). The matrix is formed by an association of amyloid proteins as scaffold and exopolysaccharides ([Zogaj et al., 2003](#)). The bacterial amyloid proteins have other functions as well: forming a physical barrier with a protective role against other species of bacteria, helping to bind each other, acting as scavengers for toxins, and providing the necessary moisture ([Blanco et al., 2012](#); [Romling, 2005](#); [Zogaj et al., 2003](#)).

Functional bacterial amyloid proteins can induce cross-seeding amyloid formation both *in vitro* and *in vivo* ([Lundmark et al., 2005](#); [Zhou et al., 2012](#)) and may be a template for human alpha-synuclein amyloid fibrils formation ([Chen et al., 2016](#); [Chorell et al., 2015](#); [Evans et al., 2015](#); [Sampson et al., 2020](#)). Interestingly, functional bacterial amyloids are recognised by the innate immune system as a pathogen-associated molecular pattern, the immune response involving toll-like receptor TLR-1 and TLR-2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and inducible nitric oxide synthase (iNOS), the same as in the case of misfolded alpha-synuclein that occurs in PD ([Daniele et al., 2015](#); [Tukel et al., 2010](#); [Tukel et al., 2005](#); [Venegas and Heneka, 2017](#)).

The most studied functional bacterial amyloid proteins in connection with the microbiota-gut-brain axis are curli, the first functional amyloid discovered, and the more recently described Fap.

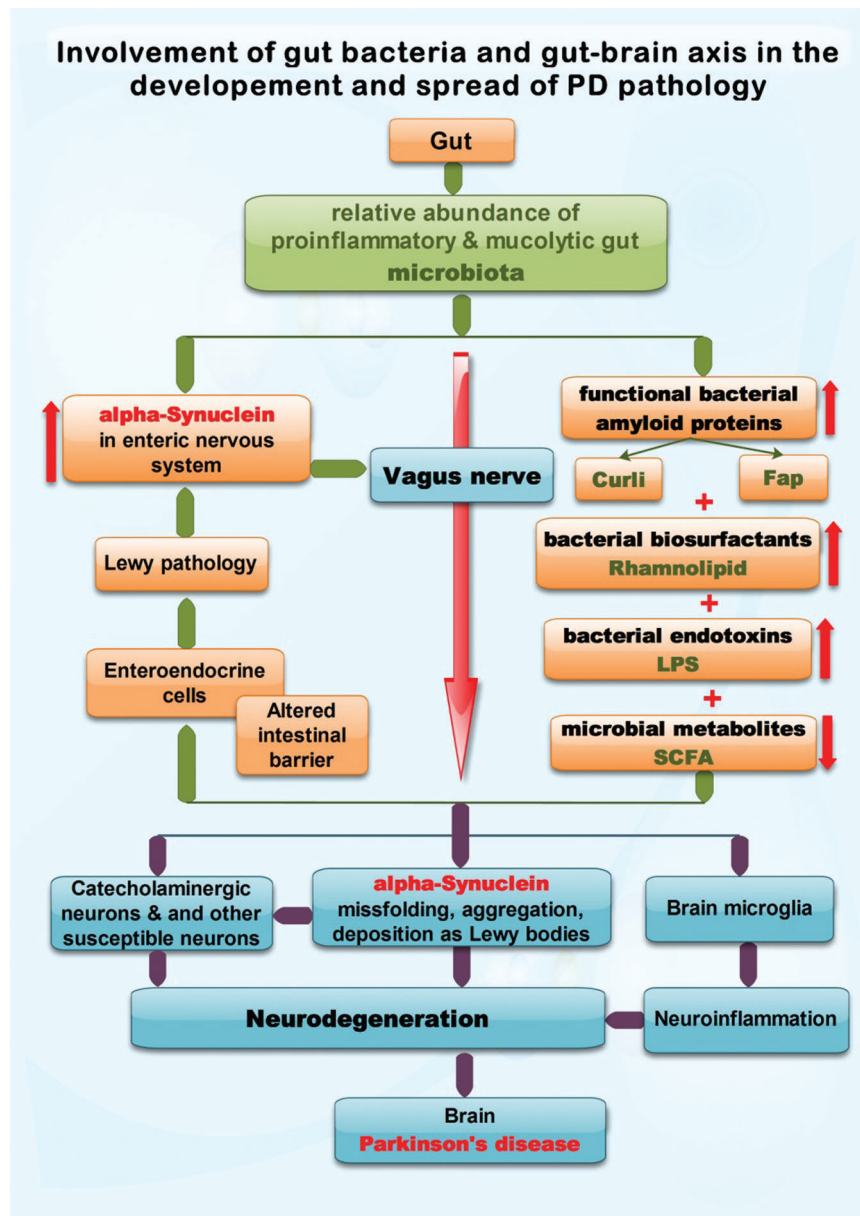
#### Curli

Curli is an extracellular protein produced by Enterobacteriaceae, especially by *E. coli* and *Salmonella* ([Evans and Chapman, 2014](#); [Olsen et al., 1989](#); [Tursi and Tukel, 2018](#); [Zogaj et al., 2003](#)). It contributes to biofilm formation, gut colonization, immune

TABLE 1

## Bacterial products that may play a role in the etiopathogeny of sporadic Parkinson's disease

Bacterial product	Possible mechanisms	Supporting evidence
Functional bacterial amyloid proteins		
<b>Curli</b> –functional bacterial amyloid protein, produced by Enterobacteriaceae (e.g., <i>E. coli</i> , <i>Salmonella</i> ); main role is in bacterial biofilm formation; the expression of the Csg subunits is highly regulated by local environmental factors and is coordinated at the level of the biofilm community.	CsgA and CsgE promote human alpha-synuclein conformational changes and fibrillation (i.e., cross-species seeding)–possibly deleterious in PD. CsgC inhibits human alpha-synuclein conformational changes–possibly beneficial/protective. May induce intestinal mucosa immune responses–possibly deleterious.	Experimental- <i>in vitro</i> studies (Chorell <i>et al.</i> , 2015; Evans <i>et al.</i> , 2015) and <i>in vivo</i> PD models (Chen <i>et al.</i> , 2016; Sampson <i>et al.</i> , 2020)
<b>Fap</b> –functional bacterial amyloid protein, produced by many <i>Pseudomonas</i> strains and other bacteria; main role is in bacterial biofilm formation.	Fap can induce alpha-synuclein conformational changes and fibrillation. Removing the three imperfect repeats of the FapC subunit slows down the fibrillation of alpha-synuclein, but does not prevent it.	Experimental- <i>in vitro</i> studies (Christensen <i>et al.</i> , 2019)
Bacterial biosurfactants		
<b>Rhamnolipid</b> –glycolipid biosurfactant produced by <i>Pseudomonas</i> and other bacteria; main roles are in modulating bacterial biofilm formation, bacterial motility and protection against monocyte-derived macrophages and polymorphonuclear leukocytes.	Rhamnolipid enhances aggregation of human alpha-synuclein, inducing formation of alpha-synuclein fibril-like structures–possibly deleterious.	Experimental- <i>in vitro</i> studies (Andersen <i>et al.</i> , 2018)
Endotoxins		
<b>Lipopolysaccharide (LPS)</b> –endotoxin produced by Gram-negative bacteria; bacterial virulence factor.	LPS increases human alpha-synuclein expression and triggers/enhances its aggregation, inducing PD-like pathology, alters the intestinal and blood-brain barriers, induces innate immunity responses and activates the microglia.	Experimental- <i>in vitro</i> studies (Bhattacharyya <i>et al.</i> , 2019) and <i>in vivo</i> PD models (Kim <i>et al.</i> , 2016; Liu and Bing, 2011)
Bacterial metabolites		
<b>Short chain fatty acids (SCFA)</b> –butyrate, acetate and propionate are the main metabolites of bacterial carbohydrate metabolism.	SCFA promote intestinal motility and maintain the integrity of the intestinal barrier (which prevents direct contact between enteric alpha-synuclein and amyloidogenic xenobiotics and the passage into circulation of substances that may have proinflammatory or neurotoxic effects); may also modulate microglia activation–possibly protective.	Experimental- <i>in vivo</i> studies (Sampson <i>et al.</i> , 2016) Human studies–reduced concentration of SCFA in PD fecal samples (Unger <i>et al.</i> , 2016); decreased butyrate production capacity of gut microbiota in PD (Cirstea <i>et al.</i> , 2020); increase of SCFA in PD plasma samples, possibly reflecting altered intestinal barrier (Shin <i>et al.</i> , 2020).
<b>Molecular hydrogen</b> –common bacterial byproduct resulting from carbohydrate fermentation; it is used for the detection of hydrogen-producing small intestine bacterial overgrowth	Molecular hydrogen easily passes membranes; it has antioxidant properties (neutralizes hydroxyl radicals); may play a role in neuroprotection; may decrease inflammation–possibly beneficial role in PD.	Experimental <i>in vivo</i> studies–in mouse and rat models molecular hydrogen may slow-down the progression of PD pathology (Fu <i>et al.</i> , 2009; Fujita <i>et al.</i> , 2009). Human studies–fecal microbiota in PD is less abundant in hydrogen-producing bacteria (Scheperjans <i>et al.</i> , 2015; Suzuki <i>et al.</i> , 2018); PD microbiota produces lower amounts of molecular hydrogen (Ostojic, 2018; Suzuki <i>et al.</i> , 2018; Yoritaka <i>et al.</i> , 2013); positive results of small pilot trial of hydrogenated water in PD (Yoritaka <i>et al.</i> , 2013).



**FIGURE 1.** Exemplifies the possible roles of functional bacterial amyloid proteins (Curli and Fap), bacterial biosurfactants, lipopolysaccharide (LPS) and short-chain fatty acids (SCFA), putatively produced by the gut microbiota, in the development and spread of sporadic Parkinson's disease (PD) pathology. PD is a proteinopathy characterized by amyloid transformation of native alpha-synuclein, with pathologic misfolding, aggregation and accumulation of aggregates (i.e., Lewy bodies, Lewy neurites) and subsequent neurodegeneration. The Braak hypothesis and dual-hit theory (see text) state that in most people with PD the alpha-synuclein misfolding process originates in the gut and olfactory mucosa, where it is initiated by an unknown pathogen. The current view is that alpha-synuclein conformational changes spread transsynaptically, from the gut and olfactory mucosa neurons to the brain, via the respective nerves, by a prion-like mechanism. In this review we focus on spreading via the vagus nerve, one of the main bidirectional communication pathways of the gut-brain axis. The presence of a proinflammatory and mucolytic microbiota in people with PD, as well as lower concentrations of SCFA, results in alteration of the intestinal barrier, possibly allowing direct contact between some gut lumen xenobiotics (such as the above mentioned bacterial products) and enteric neurons that express alpha-synuclein. Moreover, intestinal inflammatory changes may increase alpha-synuclein expression in enteric neurons. *In vitro* and *in vivo* (animal models) studies suggest that the functional bacterial amyloid proteins curli and Fap, the bacterial biosurfactant rhamnolipid and the endotoxin LPS are able to induce alpha-synuclein conformational changes and pathologic aggregation. Further details are found in [Tab. 1](#).

activation and cell invasion ([Barnhart and Chapman, 2006](#)). It may induce intestinal mucosa immune response ([Nishimori et al., 2012](#); [Oppong et al., 2015](#)) and regulate gut epithelial barrier, allowing bacterial translocation ([Oppong et al., 2013](#)). It possesses all the properties of amyloids ([Chapman et al., 2002](#); [Nilsson, 2004](#)), but it differs from disease-associated

amyloids because its beta-sheet assembly is the product of a dedicated and strictly regulated biogenesis pathway and not of pathologic misfolding ([Blanco et al., 2012](#)).

The major subunit of curli is CsgA, which is capable of self-polymerizing *in vitro*. As a result, beta-sheet-rich amyloid fibres are formed ([Chapman et al., 2002](#); [Dueholm](#)

*et al.*, 2011; Wang *et al.*, 2007). CsgA amyloids form a very stable cross-beta structure that establishes close interactions with side chains on adjacent beta-sheets (Collinson *et al.*, 1999; Chapman *et al.*, 2002; Gerstel and Romling, 2001; Nelson *et al.*, 2005; Shewmaker *et al.*, 2009). The curli fibres are very stable, resistant to protease degradation and to denaturation by detergents (Chapman *et al.*, 2002).

The potential pathologic role played by curli in PD was highlighted by an *in vivo* experiment where gut exposure to the functional bacterial amyloids curli produced by *E. coli* enhanced the aggregation of human alpha-synuclein in Fisher 344 rat brains and transgenic *Caenorhabditis elegans* muscle (Chen *et al.*, 2016). Recently, Sampson *et al.* (2020) also found that the mono-colonisation of mice that overexpress human alpha-synuclein with curli-producing *E. coli* accelerates the development of alpha-synuclein aggregation in the gut and the brain and exacerbates gastrointestinal dysfunction and motor impairment, by a curli-dependent cross-seeding mechanism; oral administration of a gut-restricted amyloid inhibitor reduced these findings (Sampson *et al.*, 2020).

#### Curli gene expression

Curli expression is controlled both on the cellular level and within the bacterial biofilm community by environmental signals and chemical gradients, like temperature, oxygen or osmolarity (Gerstel and Romling, 2001; Olsen *et al.*, 1993a; Prigent-Combarete *et al.*, 1999). The seven genes for curli (*csg*) are located in two divergently transcribed operons, *csgDEFG* and *csgBAC* (Hammar *et al.*, 1995; Rudd, 2000). One of the most complex regulated promoters of the *E. coli* genome is the *csgDEFG* (Ishihama, 2010). There is also an internal regulation of curli expression by *csgD*, the master regulator of curli biogenesis and the first gene product of *csgDEFG* operon (Evans and Chapman, 2014), which is necessary for transcription of the *csgBAC* operon. *CsgD* is a member of the FixJ/LuxR family of transcriptional regulators coordinating the expression of some biofilm components such as cellulose and curli (Brombacher *et al.*, 2003; Hammar *et al.*, 1995; Ogasawara *et al.*, 2011). The *csgDEFG* promoter expression is modulated by transcriptional regulators, such as the catabolite repressor/activator protein Cra, the cAMP receptor protein CRP, the protein RcdA (Brown *et al.*, 2001; Ogasawara *et al.*, 2010b; Reshamwala and Noronha, 2011; Shimada *et al.*, 2012; Zheng *et al.*, 2004).

In *E. coli* there are two DNA global regulatory protein complexes which modulate curli gene expression in an antagonistic way—i.e., integration host factor (IHF), which promotes curli gene expression while the histone-like protein (H-NS) represses it (Gerstel *et al.*, 2003; Ogasawara *et al.*, 2010a; Olsen *et al.*, 1993b). The regulatory proteins, both negative and positive, bind simultaneously in a competitive way. *CsgDEFG* transcript is also regulated by small regulatory ribonucleic acids (RNAs), both negatively (e.g., by *OmrA*, *OmrB*, *McaS*, *GcvB*, *RprA*) and positively (e.g., by *ArcZ*, *SdsR*) (Holmqvist *et al.*, 2010; Jorgensen *et al.*, 2013; Mika *et al.*, 2012; Monteiro *et al.*, 2012; Olsen *et al.*, 1993b).

#### Curli structure and CsgA amyloid assembly

Curli has two subunits, CsgA, the major one, and CsgB, the minor one. They are encoded by *csgBAC* operon (Collinson *et al.*, 1996, 1997; Olsen *et al.*, 1993a). CsgA is a soluble peptide, secreted across the outer membrane, in an unstructured form (Collinson *et al.*, 1991; Chapman *et al.*, 2002; Cherny *et al.*, 2005; Gibson *et al.*, 2007; Olsen *et al.*, 1993a), and together with CsgB fibrils, which act as a nucleator, it is transformed into an amyloid structure (Hammar *et al.*, 1996; Hammer *et al.*, 2007), by nucleation-precipitation (Desvaux *et al.*, 2009). *In vitro* CsgA polymerization involves three phases: A lag phase, a fibre elongation phase and a stationary phase (Chapman *et al.*, 2002; Wang *et al.*, 2007). The CsgA can adopt toxic oligomeric forms, thus the cells that assemble functional amyloids like curli developed mechanisms to limit this cytotoxicity associated with preamyloid oligomers: Employment of chaperones to prevent inappropriate aggregation; localization of amyloidogenic proteins to specific regions in or outside the cell; temporal control to minimize toxic oligomeric intermediates (Blanco *et al.*, 2012). The interactions between CsgA and other Csg components (CsgC-G) support all these mechanisms.

A third protein, CsgC, is periplasmic and is proposed to have a role in subunits secretion (Gibson *et al.*, 2007; Taylor *et al.*, 2011) and maybe in CsgA folding and assembly of the mature curli protein (Gibson *et al.*, 2007). This is a beta-sheet rich protein that has an immunoglobulin-like fold and a conserved CXC motif. Other roles presumed to be played by CsgC involve the regulation of CsgG outer membrane assembly and pore activity (Taylor *et al.*, 2011). CsgD is a protein that controls and helps biofilm formation by managing curli production (Brombacher *et al.*, 2003; Hammar *et al.*, 1995; Ogasawara *et al.*, 2011; Romling *et al.*, 2000). Proteins CsgE, CsgF, and CsgG are involved in the outer membrane secretion apparatus. CsgG participates in the formation of a pore-like structure in the outer membrane, required for secretion of CsgA and CsgB into the extracellular space (Epstein *et al.*, 2009; Narita *et al.*, 2004; Robinson *et al.*, 2006). Here, the two subunits participate to form amyloid fibres (Hammer *et al.*, 2007). CsgE and CsgF play chaperone-like functions supporting the secretion and the attachment of curli fibres to the cell surface (Nenninger *et al.*, 2011; Robinson *et al.*, 2006). CsgF membrane-associated and surface-exposed protein is essential for CsgB surface exposure and for effective CsgA polymerization (Chapman *et al.*, 2002; Epstein *et al.*, 2009; Hammer *et al.*, 2007; Nenninger *et al.*, 2009). CsgE, a periplasmic protein, is considered to direct CsgA to the CsgG pore-like structure and mediate its secretion, as it inhibits CsgA polymerization *in vitro* (Nenninger *et al.*, 2011).

#### Interaction with alpha-synuclein

The above-mentioned study of Sampson *et al.* found CsgA to be involved in human alpha-synuclein fibril formation (Sampson *et al.*, 2020). Chorell *et al.* (2015) showed that CsgE accelerates human alpha-synuclein amyloid formation.

Interestingly, CsgC was found to inhibit amyloid formation of human alpha-synuclein *in vitro* (Chorell *et al.*, 2015; Evans *et al.*, 2015).

#### Functional amyloids in *Pseudomonas* (Fap)

Other bacterial functional amyloids, analogous to curli amyloid produced by *Escherichia coli*, are functional amyloids in *Pseudomonas* (Fap), produced by many *Pseudomonas* strains (Dueholm *et al.*, 2010).

Fap expression is controlled by a single six-gene operon, *fap* (Dueholm *et al.*, 2010). Dueholm *et al.* (2013) showed that the *fap* operon is a molecular machine for functional amyloid formation. The major Fap subunit is FapC. It consists of 316 amino acid residues plus a 24-amino acid signal sequence (Bleem *et al.*, 2018; Dueholm *et al.*, 2010). Its structure includes three imperfect sequence repeats, R1-3, of 37 amino acid residues (Dueholm *et al.*, 2010), separated by two "linker" regions, L1-2 (Dueholm *et al.*, 2013). Similar to curli, Fap can induce alpha-synuclein conformational changes and fibrillation (Christensen *et al.*, 2019). Recently, Christensen *et al.* (2019) demonstrated that removing the three imperfect repeats of FapC slows down the fibrillation of alpha-synuclein, but does not prevent it.

Another Fap structure is FapB, a nucleator protein, analogous with CsgB of curli that has a 38% sequence identity to FapC and is supposed to serve as a template for rapid polymerization of the fibrils outside the cell (Bleem *et al.*, 2018; Dueholm *et al.*, 2010). The rest of the proteins encoded by the *fap* operon constitute four other subunits: FapF subunit which forms the outer membrane pores participating in amyloid precursors translocation (Rouse *et al.*, 2017), FapA subunit represented by chaperones guiding monomers through the periplasm and FapE and FapD, auxiliary regulators and proteases (Dueholm *et al.*, 2013). FapF is thought to represent a precursor of the signalling peptides called bacteriocins (Dirix *et al.*, 2004).

Barnhart and Chapman revealed that *fapA-F* function is analogous to the *E. coli* *csg* operons (*csgBAC* and *csgDEFG*) (Barnhart and Chapman, 2006). *Fap* operon does not include a transcription factor equivalent to CsgD, organization of *fap* genes into a single operon needing no internal transcription factor, as Dueholm *et al.* showed (Dueholm *et al.*, 2013). These authors proposed that Fap are extracellular biofilm components of equal importance to polysaccharides, other proteins, and extracellular DNA (Dueholm *et al.*, 2013).

Using a combination of bioinformatics and protein engineering, Bleem *et al.* (2018) examined the FapC sequence in greater detail. They identified specific motifs implicated in amyloid formation and established the particular significance of the third repeat motif in promoting fibril formation, contributing to understanding the mechanism of amyloid polymerization in *P. aeruginosa* (Bleem *et al.*, 2018). The authors observed that mutations in the third repeat of FapC, R3, reduced amyloid propensity, increasing its susceptibility to exogenous inhibitors. They also showed the existence of a disulphide bond between two monomers in a second conserved sequence region, a CXXC motif near the C-terminus of FapC, which could serve as an additional molecular reinforcement in mature fibrils.

Christensen *et al.* (2019) demonstrated that the disulphide bond formation delays fibrillation in *Pseudomonas*, but also delays fibrillation of human alpha-synuclein (Christensen *et al.*, 2019).

All the above data could be used to find effective inhibitors of fibril formation and biofilm establishment *in vivo*, as new therapeutic targets within the microbiota-gut-brain axis, with the aim of preventing or slowing down the progression of PD and other neurodegenerative conditions.

#### Biosurfactants–Rhamnolipid

There are few data regarding the rhamnolipids produced by gut bacteria and their ability to induce alpha-synuclein misfolding.

Rhamnolipids are biosurfactant glycolipids produced by bacteria like *Pseudomonas* sp., which modulate bacterial biofilms (Pamp and Tolker-Nielsen, 2007). They are composed of a glycosyl head group, mono- or di- rhamnose, and a branched carboxylated alkyl chain, beta-hydroxydecanoic acid (Lang and Wullbrandt, 1999).

Rhamnolipids have many functions, such as modulation of bacterial motility (Wang *et al.*, 2014) and bacterial biofilm development (Pamp and Tolker-Nielsen, 2007); they can modify the cell surface of bacteria (Sotirova *et al.*, 2009), participate in protein transport across the human stratum corneum (Meyer-Hoffert *et al.*, 2011) and protect against monocyte-derived macrophages and polymorphonuclear leukocytes (Van Gennip *et al.*, 2009). Although rhamnolipids are known to affect many proteins, like bovine serum albumin (Sanchez *et al.*, 2008), alpha-lactalbumin, myoglobin (Andersen and Otzen, 2014), less is known about gastrointestinal tract protein damage (Markou and Apidianakis, 2014).

Andersen *et al.* (2018) reported the impact of rhamnolipid on the aggregative behaviour of the alpha-synuclein (Andersen *et al.*, 2018). Their group showed that alpha-synuclein, which is natively unfolded, can suffer amyloid conformational changes when exposed to biosurfactants, such as the rhamnolipid produced by *P. aeruginosa* (Andersen *et al.*, 2018). The monomeric rhamnolipid enhances the ability of alpha-synuclein to permeabilize membranes, and the micellar rhamnolipid can induce the formation of a protein beta-sheet structure with a worm-like fibrillary appearance (Andersen *et al.*, 2018). Moreover, in the absence of rhamnolipid, alpha-synuclein can reduce biofilm formation by *Pseudomonas*; conversely, at physiological temperatures, rhamnolipid induces the rapid formation of alpha-synuclein fibril-like structures (Andersen *et al.*, 2018).

#### Endotoxins–Lipopolysaccharide

Research has shown a correlation between PD and alterations in gut microbiota, as well as gastrointestinal inflammation (Heintz-Buschart *et al.*, 2018; Hill-Burns *et al.*, 2017; Houser *et al.*, 2018; Houser and Tansey, 2017; Nuzum *et al.*, 2020; Schwartz *et al.*, 2018). Various studies report an increased level of pathogenic Gram-negative bacteria (Proteobacteria, *Enterobacteriaceae*, *Escherichia* sp.)

in individuals with PD (Keshavarzian *et al.*, 2015; Li *et al.*, 2017; Scheperjans *et al.*, 2015).

LPS is an endotoxin derived from Gram-negative bacteria cell walls, which is associated with increased oxidative stress and intestinal inflammation (Fang, 2016; Guo *et al.*, 2015; Loffredo *et al.*, 2020; Nighot *et al.*, 2017). LPS is composed of 3 distinct units, a hydrophobic hexa-acylated lipid A moiety, a polysaccharide domain O-antigen, and a core oligosaccharide that covalently bonds the two other entities (Bhattacharyya *et al.*, 2019). It is known that LPS can modulate alpha-synuclein aggregation *in vitro* and cause many pathological PD-like effects in experimental *in vivo* models (Kim *et al.*, 2016; Liu and Bing, 2011).

In PD, the intestinal barrier is disrupted and LPS can enter the systemic circulation (Parashar and Udayabanu, 2017). A recent study found that increased serum levels of zonulin (a protein responsible for the disassembly of intercellular tight junctions) (Ajamian *et al.*, 2019) are correlated with serum LPS in patients with neurodegenerative diseases (Loffredo *et al.*, 2020). The permeability of intestinal tight junctions may also be increased by LPS (Choi *et al.*, 2018; Fang, 2016). Alteration of the intestinal barrier could be involved in the etiopathology of PD by facilitating direct contact between enteric alpha-synuclein and amyloidogenic xenobiotics (including bacterial products of the gut microbiota, LPS itself being potentially amyloidogenic) and by allowing passage of LPS and other xenobiotics into the bloodstream – with potential neurotoxic and neuroinflammatory consequences, increasing susceptibility to neurodegeneration in the presence of misfolded alpha-synuclein (Van and Derkinderen, 2019). Moreover, LPS may also induce intestinal inflammatory changes (possibly enhanced in the presence of proinflammatory gut microbiota) and local overexpression of alpha-synuclein, as seen in animal models (Van and Derkinderen, 2019), thus increasing exposure to amyloidogenic factors.

*In vitro* studies are in agreement with the above, the exposure to LPS of IEC-6 cells resulting in a reduction and altered distribution of the tight junction markers ZO-1 (zonula occludens protein-1) and E-cadherin around the cell membrane (Gorecki *et al.*, 2019). The same study showed that *in vivo*, the administration of LPS to transgenic Thy-1- $\alpha$ Syn mice, a murine PD model, led to early motor manifestations as compared to untreated Thy-1- $\alpha$  Syn mice.

Other rodent models receiving LPS treatment exhibited hallmarks of PD pathology and other characteristic features: microglial inflammation in the substantia nigra, reduced dopamine production and motor impairments (Sharma and Nehru, 2015), increased alpha-synuclein expression (Kelly *et al.*, 2014), selective dopaminergic neuronal loss and nigrostriatal alpha-synuclein aggregation (He *et al.*, 2013). LPS induces peripheral inflammation and neuroinflammation through the TLR-4/NF- $\kappa$ B pathway, as well as the increased production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ) (Mafra and Fouque, 2015; Perez-Pardo *et al.*, 2019). The presence of proinflammatory cytokines impairs the BBB integrity and is responsible for the enhanced susceptibility to toxins from the gut (Bodea *et al.*, 2014). Over-activation of

microglia causes damage to neurons (Kannarkat *et al.*, 2013; Zhang *et al.*, 2005).

Alpha-synuclein misfolding and aggregation are favored by the inflammatory environment (Gao *et al.*, 2011). Nuclear magnetic resonance spectroscopy, Bhattacharyya *et al.* (2019) showed that the direct interaction of LPS with alpha-synuclein modulates the protein's conformation into alternative nucleating forms and stabilizes the  $\alpha$ -helical intermediates in the alpha-synuclein aggregation pathway (Bhattacharyya *et al.*, 2019). After misfolding and aggregation, alpha-synuclein is released into the extracellular space and can enter another cell, where it can serve as a template for further misfolding of monomeric alpha-synuclein (Angot and Brundin, 2009; Brundin *et al.*, 2008; Dunning *et al.*, 2012).

### Bacterial Metabolites–Short-Chain Fatty Acids and Molecular Hydrogen

Recent data show that some metabolic pathways are enriched in the faecal microbiota of people with PD, suggesting increased production capacity of potentially deleterious metabolites such as p-cresol, phenylacetylglutamine and methionine, while pathways with beneficial metabolites, such as the SCFA butyrate pathway, are reduced (Baldini *et al.*, 2020; Cirstea *et al.*, 2020). Consistent findings concern the SCFA, which we will further discuss, along with molecular hydrogen, another by-product of bacterial carbohydrate metabolism, with putative neuroprotective effects.

#### Short-chain fatty acids

SCFA are fermentation products generated by bacteria, including those in the gut microbiota, through various metabolic pathways (Sampson *et al.*, 2016). The most abundant SCFA in the human body are butyrate, acetate and propionate (Dalile *et al.*, 2019). They are used locally by colonocytes, as well as absorbed in the colon and are transported to the liver via the portal circulation (Morrison and Preston, 2016), where they are used as energy substrates for hepatocytes (Schonfeld and Wojtczak, 2016), while a minor fraction enters the systemic circulation (Boets *et al.*, 2015). SCFA maintain the integrity of the intestinal barrier, regulate intestinal motility, mucus production and several immunological processes in the body (Canani *et al.*, 2011; Lewis *et al.*, 2010; Unger *et al.*, 2016). Most SCFA can reach the CNS and cross the BBB (Perry *et al.*, 2016; Sampson *et al.*, 2016). A study on mice showed that they can decrease the permeability of the BBB and increase the expression of occludin in the BBB tight junctions (Braniste *et al.*, 2014).

Several studies have investigated the link between SCFA and PD (Cirstea *et al.*, 2020; Shin *et al.*, 2020; Unger *et al.*, 2016). Unger *et al.* (2016) found a significantly reduced concentration of acetate, propionate and butyrate in faecal samples from patients with PD compared to healthy controls. Moreover, SCFA-producing bacteria, such as *Roseburia* and *Faecalibacterium*, are more abundant in healthy individuals (Bedarf *et al.*, 2017; Hopfner *et al.*, 2017; Keshavarzian *et al.*, 2015; Li *et al.*, 2017; Nishiwaki *et al.*, 2020; Nuzum *et al.*, 2020).

Administration of sodium butyrate (a histone deacetylase inhibitor) has proven beneficial in animal models of PD,



improving motor impairment and dopamine deficiency (Paiva *et al.*, 2017; Sharma *et al.*, 2015; St Laurent *et al.*, 2013). However, in germ-free mice overexpressing alpha-synuclein, administration of SCFA led to microglia activation, alpha-synuclein aggregate formation and neuroinflammation (Sampson *et al.*, 2016). A recent study analysed the possible remote effects of SCFA on the CNS, by measuring their plasma concentration (Shin *et al.*, 2020). In contrast to faecal samples, plasma SCFA were increased in PD, the authors suggesting that this paradoxical finding could be the result of intestinal wall leakage caused by gut dysbiosis and local low-grade inflammation (Shin *et al.*, 2020).

Gut microbial composition and SCFA production can be regulated indirectly by the ingestion of probiotics or prebiotics, the latter acting as a substrate for bacteria in the colon (Gibson *et al.*, 2017; Leblanc *et al.*, 2017; Sanders, 2008). Diet can also positively influence the microbiome and it has been suggested that a vegetarian diet increases the availability of fermentable substrates and may have a beneficial effect on the clinical course of PD (Derrien and Veiga, 2017; Hegelmaier *et al.*, 2020; Klimentko *et al.*, 2018; Martinez *et al.*, 2013; Wong *et al.*, 2018).

#### Molecular hydrogen

Molecular hydrogen is a common bacterial by-product resulting from carbohydrate fermentation. It is produced by the human gut microbiota and easily crosses membranes, reaching the bloodstream and being exhaled – thus its use in the hydrogen breath test for the detection of small intestine bacterial overgrowth (SIBO) (Ostojic, 2018). It has antioxidant properties, neutralizing hydroxyl radicals, and may decrease inflammation, with putative neuroprotective effects (Ohta, 2014).

Experimental evidence coming from mouse and rat models suggest that molecular hydrogen may slow down the progression of PD pathology (Fu *et al.*, 2009; Fujita *et al.*, 2009). Moreover, a small pilot double-blind placebo-controlled randomized trial found that 1 litre of hydrogenated water per day improves motor outcomes in people with PD, at 48 weeks (Yoritaka *et al.*, 2013). Other data from human studies suggest that the faecal microbiota of people with PD is less abundant in hydrogen-producing bacteria (e.g., *Prevotella*) compared to that of healthy controls (Scheperjans *et al.*, 2015; Suzuki *et al.*, 2018). Small studies also suggest that the small intestine microbiota of people with PD may produce lower amounts of molecular hydrogen, as measured in the exhaled air (Ostojic, 2018; Suzuki *et al.*, 2018; Yoritaka *et al.*, 2013).

#### Conclusions

An increasing number of studies suggest that sporadic PD may start in the gut and olfactory mucosa, Lewy pathology spreading to the brain, via the vagus and olfactory nerves, through a prion-like mechanism.

Gut dysbiosis is present in people with PD compared to healthy controls, but the causality relation between the composition and function of the gut microbiota and sporadic PD has not been proven yet. In this review we brought together the latest data, coming mostly from *in*

*vitro* studies and animal models, regarding the bacterial products that can trigger alpha-synuclein misfolding in experimental settings and thus may be involved in the etiopathogeny of sporadic PD. Available evidence suggests that products of bacteria found in the gut may result in alteration of the intestinal barrier, may lead to overexpression of enteric alpha-synuclein and may play key roles in triggering alpha-synuclein self-propagating misfolding events that result in alpha-synuclein self-aggregation and formation of Lewy bodies. Microbiota products that enter the bloodstream may also have neuroinflammatory and neurotoxic effects and may interfere with neuroprotection pathways, modulating neuronal susceptibility to neurodegeneration.

Currently, there are no disease-modifying treatments for neurodegenerative conditions, including PD. Amyloidogenic bacterial products, especially functional bacterial amyloid proteins, biosurfactants and endotoxins are possible triggers of the initial pathologic alpha-synuclein misfolding in sporadic PD, making them potentially attractive therapeutic targets for preventing or slowing down the progression of the disease. This theory however has a series of limitations, mainly related to the lack of direct evidence on the interaction between the amyloidogenic bacterial products and alpha-synuclein within the human gut. Further research is needed.

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