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REVIEW

Role of the Gut Microbiome and Bacterial Amyloids in the Development of Synucleinopathies

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Abstract—Less than ten years ago, evidence began to accumulate about association between the changes in the composition of gut microbiota and development of human synucleinopathies, in particular sporadic form of Parkinson's disease. We collected data from more than one hundred and thirty experimental studies that reported similar results and summarized the frequencies of detection of different groups of bacteria in these studies. It is important to note that it is extremely rare that a unidirectional change in the population of one or another group of microorganisms (only an elevation or only a reduction) was detected in the patients with Parkinson's disease. However, we were able to identify several groups of bacteria that were overrepresented in the patients with Parkinson's disease in the analyzed studies. There are various hypotheses about the molecular mechanisms that explain such relationships. Usually, α-synuclein aggregation is associated with the development of inflammatory processes that occur in response to the changes in the microbiome. However, experimental evidence is accumulating on the influence of bacterial proteins, including amyloids (curli), as well as various metabolites, on the α-synuclein aggregation. In the review, we provided up-to-date information about such examples.

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INTRODUCTION. αSyn PROTEIN AND SYNUCLEINOPATHIES

Interest in synuclein proteins increased significantly after discovery of genetic and neuropathological association between α-synuclein (αSyn, encoded by the *SNCA* gene) [1] and Parkinson's disease (PD). Protein αSyn is a major component of the pathological protein aggregates inside neurons, Lewi bodies. Presence of such aggregates is one of diagnostic signs of PD [2]. At present, β- and γ-synucleins have also been identified [3, 4]. Similar to αSyn, they are small soluble proteins present predominantly in the nervous tissue cells and in some tumors in vertebrates [3]. The αSyn protein consists of 140 aa [5, 6]. There are three domains in its composition: N-terminal region (1-60 aa), which is bound to a cell membrane; hydrophobic region known as non-amyloid component (NAC, 61-95 aa), and C-terminal hydrophilic region (96-140 aa) [6-8]. It is known that αSyn facilitates decrease of apoptosis in dopaminergic neurons [9], prevents oxidation of unsaturated fatty acids [10], regulates transport of synaptic vesicles at presynaptic terminals [11], participates in formation of the SNARE complex (soluble NSF (N-ethylmaleimide-

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; aSyn, α-synuclein; CNS, central nervous system; ENS, enteric nervous system; GIT, gastrointestinal tract; LPS, lipopolysaccharides; NS, nervous system; PD, Parkinson's disease; PNS, peripheral nervous system; SCFA, short-chain fatty acids; sPD, sporadic Parkinson's disease.

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sensitive factor) attachment receptor) [12] and in the clathrin-mediated endocytosis [13]. Nevertheless, all functions of the αSyn protein have not been elucidated yet.

Aggregation of the αSyn protein. Despite the numerous existing studies, structure of αSyn under physiological conditions has not been fully elucidated yet. It is assumed that in cytosol this protein exists predominantly as an unfolded monomer [14]. Aggregation propensity has been shown for the αSyn protein; therefore, it can form both oligomers and fibrils [15]. These complexes could have typical cross-β-structure and exhibit other properties common to amyloids [16, 17].

Various factors could affect the process of αSyn aggregation including acidity [18], temperature [19], molecular crowding (effect of reduction of free cytoplasmic volume in the cell and increase of concentration of molecules [20], metal ions (such as aluminum, copper, iron, cobalt, and manganese) [19], organic solvents [21], pesticides [19], αSyn-binding proteins [22-24], exosome lipids [25], and others. Moreover, neurotoxicity of αSyn and its aggregation could be affected by post-translational modifications, such as phosphorylation [26, 27], ubiquitination [28], nitration [29], SUMOylation [30], proteolysis [31], and N-terminal acetylation [32]. Most of the aggregates of αSyn (90%) found in Lewi bodies contain protein phosphorylated at the S129 residue [33]. However, it is still unclear whether the αSyn phosphorylation stimulates its aggregation or prevents this as well as whether it affects αSyn neurotoxicity [34]. Role of glycation in the development of synucleinopathies is also seems controversial. On the one hand, the protein with this modification has been identified in the frontal cortex of the patients with PD [35, 36], while its level is elevated in the blood of these patients [37]. On the other hand, the glycated monomeric or oligomeric αSyn do not form fibrils on its own, prevent aggregation of non-modified protein [38, 39], as well as are incorporated into the αSyn fibrils to a lesser degree [40].

Different chaperons, including the ones from bacteria, also affect αSyn aggregation. The CsgC and DnaK proteins from *Escherichia coli* inhibit this process [41, 42], while the SlyD and DnaJ proteins, on the contrary, stimulate aggregation [42, 43]. The human chaperon FKBP12, belonging to the same protein family as SlyD, also accelerates formation of the αSyn amyloid aggregates [43].

The results of experiments with animal models and cell cultures, including neuronal cell cultures, indicate pathogenic role of αSyn aggregation that causes disruption of synaptic transmission, functioning of mitochondria and endoplasmic reticulum, initiates defective autophagy, neuroinflammation, and oxidative stress [44, 45]. It has been also suggested that the αSyn aggregation in presynaptic terminals affects assembly of the SNARE complexes, thus reducing efficiency of dopamine release [46]. Moreover, some synaptic proteins and receptors of neurotransmitters, such as, for example, N-methyl-D-aspartic acid receptors (NMDA), were identified as presumed αSyn partners [47]. In particular, it was shown that αSyn co-aggregated with the nitric oxide synthase 1 (neuronal) adaptor protein (NOS1AP or CAPON), which indirectly interact with the NMDA-receptors [24].

Prion-like properties of the αSyn protein. In the strict sense mammalian prions are infectious agents in which the PrP^{Sc} protein with altered conformation recruits and transforms its normal analogue PrP^{C}, thus creating self-propagating protein particles with misfolded structure, which could be transmitted from cell to cell [48, 49]. It has been suggested that some amyloid proteins have the similar prion-like propagation mechanism. In addition to αSyn, existence of prion properties has been suggested for other known amyloids such as β-amyloid (Aβ) [50], Tau [51], and huntingtin [52].

Prion mechanism of neurodegeneration development in PD was first suggested in the studies by Braak et al. [53, 54] based on the distribution of pathological changes associated with αSyn aggregation in the brain of the patients with PD. Later the proof of prion-like propagation of αSyn was obtained as a result of observation of this protein aggregation in the transplanted tissues several years after surgery; in particular, transfer of the Lewy pathology from the host to transplant was detected [55, 56]. Since then, it was shown in different studies that the αSyn fibrils obtained from the recombinant protein or from the lysates isolated from the disease-affected brain could propagate in a prion-like manner in the different types of human cell cultures [57-59] and in the rodent brains [60-63]. Several mechanisms of αSyn propagation have been suggested in response to the question how the transfer of αSyn between the cells occurs. For example, there are indications that the αSyn monomers, oligomers, and fibrils could be transported with the help of vesicles from the donor cell via exocytosis followed by release into the extracellular space and capture by the acceptor cells [64, 65].

Synucleinopathies are a group of neurodegenerative diseases characterized by the presence of inclusions in neurons and/or glia consisting of aggregated αSyn [66]. From the point of view of pathomorphology synucleinopathies could be divided into two main groups: multiple system atrophy (MSA) and diseases associated with formation of Lewy bodies [67, 68].

MSA could be subdivided into two main subtypes: olivopontocerebellar atrophy and striatonigral degeneration. MSA is an impaired movement disease characterized with various combinations of vegetative state,

parkinsonism, cerebellar ataxia, pyramidal signs, and non-motor symptoms [69].

Pathologies with Lewy bodies are subdivided into three main clinical pathological subtypes: PD, PD dementia, and Lewy body dementia. However, Lewy bodies and αSyn aggregates are found also in a number of neurometabolic diseases such as PLA2G6-associated neurodegeneration, POLG-associated neurodegeneration, Niemann–Pick type C disease, and Krabbe disease [70], as well as in the patients with Alzheimer's disease (AD) [71]. Moreover, αSyn amyloid aggregates have been observed in axonal spheroids in neuroaxonal dystrophies [72]. PD symptomatic will be considered below, but it is worth mentioning that in the majority of PD patients (around 83%) at the later stages it develops into PD dementia [73]. The symptoms of dementia with Lewy bodies include dementia, neurocognitive changes, parkinsonism, visual hallucinations, and disruption of behavior in the rapid eye movement phase of sleep [74].

There are two forms of PD: sporadic PD (sPD) with unknown etiology and familial PD with known genetic etiology [75]. In the latter case replacements in amino acid sequence of αSyn have been identified (e.g., A53T, A30P, E46K, A53E), which are associated with autosomal dominant forms of PD [76-79]. In addition, familial PD is caused by duplication and triplication of the *SNCA* gene [80, 81]. Some mutations in other genes are also considered as risk factors for PD development. Among these the *LRRK2* gene (encodes leucine-rich repeat kinase 2, LRRK2) has been identified, expression of which increases in the inflamed colon tissues of the patients with PD and Crohn's disease, as well as in the cells of peripheral immune system [82]. Other genes mutations in which are associated with PD are *PINK1* (encodes phosphatase and tensin homolog-induced kinase 1, PINK1) and *PRKN* (encodes ubiquitin ligase parkin, parkin), which play a key role in adaptive immunity repressing presentation of mitochondrial antigens, i.e., are repressor of autoimmune mechanisms. Mutations in these genes cause mitochondrial dysfunctions in some forms of PD [83].

PD is accompanied by a number of symptoms, which are subdivided into movement (motor) and non-movement. Motor symptoms include tremor and limb rigidity, slowness of movement (bradykinesia), and gait impairment. Non-motor symptoms are manifested as neuropsychic disorders, problems with sleeping, depression, physical and mental fatigue, as well as sensory disorders: vision dysfunction associated with rapid movements of eyeballs, hyposmia (decreased sense of smell) [84-86]. In the majority of cases non-motor symptoms are manifested much earlier than the motor symptoms, which raises the question on where exactly development of synucleinopathies starts: in the peripheral (PNS) or central nervous system (CNS) [87].

It must be mentioned in the context of this review that some gastrointestinal disorders are observed in the patients with PD (with sPD, in particular) such as excessive salivation, dysphagia, difficulties with gastric emptying, constipation, and problems with defecation [84]. These symptoms are often accompanied by changes in the gut microbiome (dysbiosis) [88-90]. Examples of association between dysbiosis and development of synucleinopathies will be discussed in more detail further in the review. The term "dysbiosis" will be used in a broader sense for the cases when either increase or decrease of certain groups of microorganisms occurs. Otherwise, a particular effect will be mentioned. The term "microbiome" will be used for the microbial community (microbiota) in the certain habitat with particular physicochemical properties. It must be noted that this notion includes not only live objects, but also products of their metabolism [91].

CHANGES IN MICROBIOME ASSOCIATED WITH THE DEVELOPMENT OF SYNUCLEINOPATHIES

Human gut microbiome. In order to elucidate what changes occur in microbiome of gastrointestinal tract (GIT) of the patients with PD, it is necessary to consider first composition of gastrointestinal microbiota in healthy individuals. It is currently recognized by the scientists that human microbiota is a set of all microorganisms populating human body [92]. It includes bacteria, archaea, single-cell eukaryotes (fungi and protozoa), and viruses; and it is directly involved in maintenance of healthy functioning of an organism, which allows considering it as a 'hidden organ' in a human organism [93].

Two methods are currently used for investigation of the human microbiome. The first one is amplicon sequencing of the variable region V3-V4 of the 16S ribosomal RNA (rRNA), which allows characterizing composition of bacteria and archaea at the taxonomic level and identifying structural changes in the microbial communities. However, this method does not allow one to determine differences at the species level. Shotgun metagenomic sequencing allows more detailed assessment of the microbiome composition as well as to achieve accurate taxonomic classification and determine functions of bacteria [94]. Various strategies used for analysis of metagenomics data sets are based on the reference databases; hence, there is a need in large well-characterized collections of the reference microbial genomes. At present results of numerous large-scale studies devoted to deciphering composition of the human gut microbiota have been reported [94-98].

Microbiota can be subdivided into oral, skin, gut, and respiratory microbiota; it has been considered that

the gut microbiota is the most important in the context of maintenance of health of the whole organism and has the most diverse species composition [93, 97]. Current understanding of the human gut microbial community is primarily limited by the taxonomic features at the genus level [97]. Nevertheless, according to various estimates, human gut microbiota includes from 200 to more than 1000 bacterial species [99-101]. It has been shown that the healthy human gut microbiota mainly consists of the representatives of the following bacterial phyla: Bacillota (Firmicutes), Bacteroidota (Bacteroidetes), Actinomycetota (Actinobacteria), Pseudomonadota (Proteobacteria), Fusobacteriota (Fusobacteria), and Verrucomicrobiota (Verrucomicrobia) [102], among which Bacillota and Bacteroidota are predominant [99, 102, 103] or, according to other studies, Bacillota and Actinomycetota [104]. Fungi species such as *Candida*, *Saccharomyces*, *Malassezia*, and *Cladosporium* [105] and archaea (primarily methanogenic), among which the *Methanobrevibacter smithii* species is predominant [100, 106, 107], have been also found in the composition of human gut microbiota.

Despite the existence of numerous studies devoted to investigation of the 'healthy' microbiome, there is no exact definition of this notion [108]. It is commonly recognized that under normal conditions microbiome is characterized with a wide diversity of microorganisms and persistent predominance of two key phyla: Bacillota and Bacteroidota [109]. In a number of cases description of the 'healthy' microbiome with the help of sequencing reveals also diversity of the genes involved in maintenance of symbiosis with the host organism [93, 110]. It must be mentioned that relative distribution of microorganisms is unique for every individual, and could be subjected to changes within the individual under effects of various factors. Human microbiome could be affected by the following factors: sex, age, diet, antibiotics, state of the environment, ethnic background, and many other factors [93, 110, 111]. Understanding composition of the healthy human microbiota could facilitate development of effective strategies for microbiome manipulation for therapeutic purposes. At present several methods are used including the most popular transplantation of gut microbiota and administration of prebiotics, probiotics, or symbiotic [92].

Gut microbiota participates in a number of biological processes. First of all, it allows effective extraction of energy and nutrients from food due to the presence of universal 'metabolic' genes, products of which participate in different enzymatic reactions and biochemical pathways [112]. Gut microbiota is capable of metabolizing polysaccharides and short-chain fatty acids (SCFA), majority of which are represented by acetates, butyrates, or propionates. They serve as an energy source for gut epithelium and liver [93, 113, 114]. Synthesis of biologically active molecules such as vitamins, amino acids, and lipids is realized with direct participation of gut microbiota [93].

Gut microbiota plays protective role in the human organism. It protects not only from external pathogens by producing antimicrobial substances but also serves as an important component in the development of gut mucus and immune system [93]. It is important to note in the context of this review that gut microbiota also is directly involved in immunomodulation, such as in regulation of inflammation processes. For example, microbiota mediates neutrophil migration, which further affects differentiation of T-lymphocytes into different types of regulatory and helper T-cells [115]. Dysbalance of gut microflora could result in the development of autoimmune diseases [116]. In addition, microorganisms themselves are able to produce a number of molecules, such as defensins, which facilitate enhancement of inflammation processes [117]. The data are also available indicating role of microbiota in supporting functions of the $CD8^+$ T-lymphocytes [118].

No less important role of microbiota is maintenance of the constant state of the internal environment via interaction with the brain. This interaction has been termed gut-brain axis and is a bidirectional system of signaling pathways involving the vagus nerve, immune system, and bacterial metabolites [119]. SCFA produced by the gut microbiota are capable of affecting release of mucosa neurotransmitters [120], modulation of neurotransmitters [121], and functioning of parasympathetic nervous system (NS) [122]. In addition, gut microbiota could affect functioning of afferent sensory neurons by, for example, increasing their excitability through inhibition of calcium-dependent channels as observed in the case of *Lactobacillus reuteri* [123].

Microbiota and neurodegenerative diseases. There are numerous examples of association of microbiome changes with different diseases including neurodegenerative ones. The examples include Crohn's disease [124], irritable bowel syndrome [125], colon cancer [126], AD [127], diabetes [128], obesity [129], and rheumatoid arthritis [130]. Further, we will present several examples of association of microbiome and development of neurodegenerative diseases.

AD is a neurodegenerative disease leading to progressive cognitive dysfunction [131]. Microbiome of the AD patients is enriched with bacteria of the *Escherichia* and *Shigella* genera, which cause proinflammatory state and decrease concentration of *Eubacterium rectale* exhibiting anti-inflammatory activity [132]. It is also known that bacterial lipopolysaccharides (LPS) could initiate formation of Aβ fibrils [133, 134]. These and other data allowed suggesting that some bacteria could secrete a large amount of LPS and amyloid proteins, which are capable of crossing gut- and blood-

brain barriers, which are weakening with aging or in disease, as well as indirectly affect crossing of these protective physiological barriers by the pro-inflammatory cytokines leading to AD development [131, 135].

Gut dysbiosis is considered as an important factor affecting pathogenesis of multiple sclerosis, which is an immune-mediated chronic neurological disease associated with demyelination, axon damage, and neurodegeneration [136]. Decrease of the number of bacteria associated with anti-inflammatory response has been observed in the patients with relapsing-remitting multiple sclerosis, as well as increase of the number of bacteria responsible for pro-inflammatory reactions [137].

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease associated with the death of neurons in the brain and spinal cord, as well as motor neurons. Decrease of the level of various bacteria producing butyrate (such as *Butyrivibrio fibrosolvens*, *Oscillibacter*, *Anaerostipes*) has been observed in the gut of the ALS patients and of the transgenic mice used for modeling this disease [138-140]. Moreover, it was shown that addition of butyrate to drinking water of the mice used as a model for studying ALS slows down the disease development [141].

Hence, many examples are known demonstrating the role of microbiome or its metabolites in the development of neurodegenerative diseases. Various hypotheses have been suggested for the possible mechanisms underlying these phenomena. In the following sections the role of microbiome in the development of synucleinopathies will be considered in more details as well as hypotheses explaining these interconnections.

Association between gut microbiome and synucleinopathies. The relationship between the changes in gut microbiome and PD has been first reported in the literature in 2015 [142]. It was shown in this study that the patients with PD have reduced content of bacteria from the Prevotellaceae family, and it was concluded that gut microbiome changes in PD, which leads to motor dysfunction. Later two more studies have been published: in one study the authors demonstrated that the patients with PD have reduced amount of 'anti-inflammatory' bacteria producing butyrates from the *Blautia*, *Coprococcus*, and *Roseburia* genera [143]. In another study the authors demonstrated association of PD with other groups of bacteria; in particular the amount of bacteria of *Lactobacillus* genus was higher, while the total amount of analyzed bacteria *Clostridium coccoides* and *Bacteroides fragilis* was lower than in the control. Furthermore, increased gut permeability was assumed for the patients with PD based on the analysis of the levels of LPS-binding protein and diamine oxidase in the blood serum. Supposedly, this could either promote development of dysbiosis and progression of PD, or be the result of dysbiosis [144]. These studies laid foundation for the hypothesis implying that dysbiosis could be the cause of neuroinflammation, which results in misfolding of αSyn and development of PD. After that for almost 10 years interest in this hypothesis was increasing steadily: a large amount of scientific studies with the results of metagenomic investigation of GIT of the patients with PD and other synucleinopathies was published. Search of PubMed revealed more than 130 experimental studies devoted to PD (date of access: 04.12.2022).

Apparently, the number of studies will continue to grow, especially considering the fact that certain contradictions are often being reported. For example, there is a difference in indicators of microbiome diversity within one group – PD or control (the so-called α-diversity): some studies report decrease of diversity in the patients with PD in comparison with the control group of healthy individuals [145, 146]; in others, on the contrary, either increase of diversity was demonstrated [147] or absence of differences [148]. At the same time, at the level of β-diversity (difference in composition of microbiota between the samples or groups) majority of the microbiome studies of the patients with PD are characterized with the significant change of composition in comparison with the control. In order to summarize current results on the issue, we analyzed the literature and presented all reported associations of the changes in microbiome composition with PD as a phylogenetic tree (Fig. 1). Despite the fact that there were significant differences between the analyzed studies investigating changes in the gut microbiome in PD including study design, ratio of sexes, age, duration of the disease, and others, in our analysis we did not concentrate on the cited differences, and used all statistically reliable association in our analysis. According to these data, representatives of the phyla Bacillota and Bacteroidota are most often associated with PD, moreover, for both cases associations were demonstrated both for the decrease and for the increase of the number of these microorganisms. In general, this could be expected, because the investigated groups form the basis of the human microbiome.

We also analyzed associations at the level of bacterial families in order to analyze potential causes of dysbiosis in PD (Fig. 1). Typically, multidirectional associations have been shown for many families, as well as for the larger taxonomic groups. Both reduction and increase of population of a particular group have been associated with PD development. The following families have been reported most often to have changed population (either elevated or reduced) in the patients with PD: Lactobacillaceae, Bifidobacteriaceae, Desulfovibrionaceae, Akkermansiaceae, Rikenellaceae, Verrucomicrobiaceae, Porphyromonadaceae, Tannerelaceae, and Enterobacteriaceae. The reduced population in composition of microbiome is typical for the

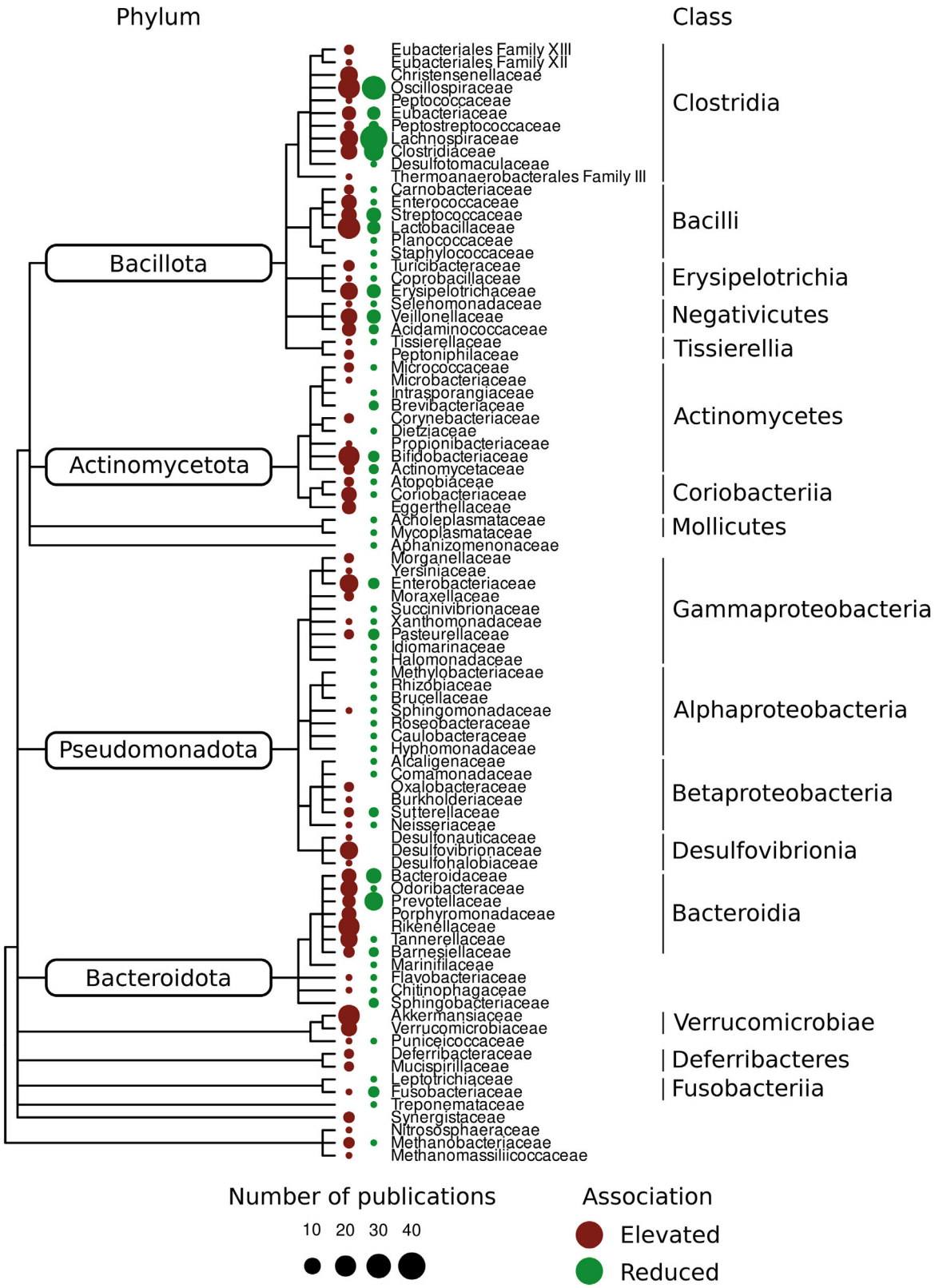

Fig. 1. Known associations between the changes of microbiome and development of PD. Taxonomic tree of bacterial families in human microbiome (according to NCBI Taxonomy database) with marked numbers of the cases of described associations (publications) or representatives of the respective family with PD. Cases in which increase or decrease of the population of particular groups of bacteria are observed are considered separately. Search of publications was conducted in the PubMed database (accessed on 04.12.2022; search query was similar to the one in the study by Toh et al., 2022: ("Microbiota" OR "Microbiome" OR "Microflora" OR "Dysbiosis") AND ("Parkinson" OR "Parkinsonism") [149]. 138 experimental papers from the total list of 1061 publications were analyzed. Classes with two or more identified families are shown, as well as most represented bacterial phyla.

representatives of the Oscillospiraceae, Lachnospiraceae, Clostridiaceae, and Prevotellaceae families. It must be noted that unidirectional changes of population (only elevated or reduced) of any particular group have been observed rarely in the patients with PD. The families Eggerthellaceae, Desulfovibrionaceae, Porphyromonadaceae, Rikenellaceae, Akkermansiaceae, and Verrucomicrobiaceae (shown only the families with representatives in a large number of independent studies) are the exception.

According to the literature data, reduction of bacterial taxa associated with anti-inflammatory/neuroprotective effects was shown in general for PD, especially in the Lachnospiraceae family and the key members such as *Butyrivibrio*, *Pseudobutyrivibrio*, *Coprococcus*, and *Blautia* [150]. Changes in representation of the Lachnospiraceae family correlate with the changed rate of metabolism in PD [150]. Several members of the Lachnospiraceae family attract attention due to their ability to produce SCFA [151].

Summarizing available information on the changes in microbiome composition in PD allowed us to reveal general pattern, in particular, to identify key taxa, which presumably contribute to the development of intestinal symptoms. At the same time there are many bacterial species for which association with PD have been shown only in few publications, therefore, further studies of human gut metagenome are needed, especially the ones using shotgun sequencing, which allow elucidating strain-level composition of microbial community. This could facilitate deciphering mechanisms of dysbiosis development in PD and to develop treatment methods.

POSSIBLE MECHANISMS OF SYNUCLEINOPATHIES DEVELOPMENT ASSOCIATED WITH DYSBIOSIS

Braak's hypothesis on misfolding of αSyn in a gut. αSyn aggregates have been detected not only in CNS, but also in PNS, such as, for example, in the part innervating gut. The hypothesis on the sPD development occurring as a result of aggregation of αSyn in the intestine neurons followed by propagation of the pathology to CNS was first suggested by Braak et al. [53, 54]. In their study the authors investigated localization of αSyn aggregates in different parts of NS of the patients with sPD. In particular, the samples of enteric nervous system (ENS), dorsal motor nuclei of the vagus nerve, substantia nigra, temporal mesocortex, and neocortex. One of the important observations was the fact that in all cases accumulation of αSyn was detected in ENS and in vagus nerve, while correlation between the presence of aggregates and stage of the disease was observed in the remaining zones. The αSyn aggregates in neocortex were found only in the patients at the latest stage of the disease development [54]. This hypothesis is in good agreement with the results of a number of publications. Lewy bodies have been found in myenteric and submucosal plexus of the intestine in the patients with PD [152, 153]. Presence of αSyn in the vagus neurons innervating intestine also has been demonstrated experimentally [154]. For example, accumulations of αSyn are found in the biopsy samples of the intestine from the patients with PD including those at the early stages of the disease, as well as prior to the development of symptoms [155-157]. The data are also available demonstrating that vagotomy decreases the risk of PD development [158]. Experimental proof of the αSyn aggregates transfer from the gut to brain has been obtained in rats. The animals were injected with the protein lysates derived from the PD patients or recombinant human αSyn into the intestine wall. After that presence of this protein was analyzed in different parts of the vagus nerve at different intervals [159]. In the experiments with mice, it was possible to achieve aggregation of αSyn in the gut by administration of rotenone (isoflavone used as a broad-spectrum insecticide and pesticide), as well as to demonstrate that the aggregates appear with time in the spinal cord and brain [160]. Different variants of the factors triggering aggregation of αSyn in the gut have been considered including presence of pathogens or viruses [161]. Prion-like properties of αSyn discussed in detail in the subsection "Prion-like properties of the αSyn protein" also support the notion that synucleinopathies could start in PNS followed by the transfer to CNS.

The data are available that contradict the Braak's hypothesis. In particular, examination of the patients with Lewy pathology did not reveal any cases with only PNS affected (place of the start of pathology according to the Braak's hypothesis), i.e., accumulation of αSyn is also found both in ENS and CNS [162]. On the other hand, there is an opinion that such observations could be false-negative due to insufficient sample size [87].

Another hypothesis has been proposed after the Braak's hypothesis suggesting that the first stages of synucleinopathy development could affect olfactory system and start there, in the olfactory bulbs. This was the start of expansion of the Braak's hypothesis development recognized as a dual-hit hypothesis [161]. At present there is no consensus on where and when aggregation of αSyn begins, although the Braak's hypothesis remains to be the one most often cited [87].

Relationship between αSyn and GIT symptoms. In the last 20 years since introduction of the Braak's hypothesis various molecular mechanisms have been suggested explaining development of synucleinopathy in ENS or emergence of the respective symptoms. One of them is associated with the presumed role of αSyn as an immunomodulator. It was shown in several stud-

ies that this protein can stimulate microglia cells or monocytes to produce inflammatory cytokines (TNFα, IL-1β) [163, 164]. Monomeric or oligomeric αSyn stimulated attraction of neutrophils and monocytes, as well as maturation of dendritic cells. Positive correlation between the intestine inflammation and αSyn expression has also been established. It has been suggested in the study that the αSyn secretion served as a stimulus for initiation of inflammatory processes [165]. Increase of the αSyn expression is a factor promoting development of PD, which previously was shown for the patients with several copies of the *SNCA* locus [80, 81]; this could explain development of synucleinopathy. On the other hand, overexpression of αSyn could inhibit release of neurotransmitters and neuromediators (dopamine, acetylcholine, noradrenaline, and others), and, due to this affect functioning of the intestine [166].

αSyn protein could induce increased expression of the genes of Toll-like receptor (TLR) and pro-inflammatory cytokine in microglia cells. TLRs participate in innate immune response and recognize the most abundant bacterial LPS. Activation of TLR-signaling could result in apoptosis of dopaminergic neurons. Moreover, activation of microglia, in turn, increases production of nitrogen oxide (NO), and, further development of synucleinopathy could proceed due to nitration of αSyn in the neighboring neurons and their apoptosis [167]. This modification also potentially stimulates formation of αSyn oligomers, and protein with such modification has been found in Lewy bodies in the patients with PD [168]. Increased content of NO-synthase has been demonstrated in the model mice with induced inflammation, which results in enhanced aggregation of αSyn [169].

Various compounds appearing in GIT could provoke PD development; among the examples different xenobiotics (herbicides, pesticides) could be mentioned [170, 171]. It was shown in the mouse model that these compounds could lead to the death of dopaminergic neurons and development of PD [172]. Indirect confirmation of this hypothesis could be provided by the fact that activation of the pathway of degradation of xenobiotics in the gut of the patients with PD has been demonstrated [173]. Supposedly, some antibiotics affect PD pathogenesis helping bacteria producing curli. Antibiotics in general decrease microbial diversity in the gut, modulate the Bacillota/Bacteroidota ratio, which results in the excessive growth of opportunistic pathogens [174]. Some bacterial metabolites such as β-N-methylamino-L-alanine could also promote PD development [175]. SCFA produced by bacteria also could cause PD symptoms. This was demonstrated with the transgenic mice overproducing αSyn and lacking their own microbiota. Administration of these compounds to animals with feed was observed to activate microglia, aggregation of αSyn, as well as development motor symptoms typical for PD. The authors suggest that in this case microglia activation is a key element of the cascade leading to the development of the disease [176]. This is in agreement with the earlier data indicating that the inflammatory processes induced by injection of LPS stimulate aggregation of αSyn in transgenic mice producing human αSyn with A53T replacement [169].

Gastrointestinal mucosa located under the epithelial layer, which is part of the blood-brain barrier, is an important factor protecting against the PD development. Normal gut microflora and its metabolites are also components of this barrier; hence, dysbiosis could facilitate penetration of pathogenic bacteria through the tight junctions into Peyer's patches. As a result, intestine becomes inflamed, which could result in the inflammatory process in PNS and emergence of PD symptoms [177]. On the other hand, as mentioned above, inflammation could cause overproduction of αSyn.

αSyn aggregation in the presence of amyloids. The hypothesis of synucleinopathy development through GIT has been considered above. However, the question remains how αSyn aggregates are formed in the intestine neurons. The reason for this, likely, lies in the possibility to induce αSyn aggregation with the help of other amyloid aggregates, which could be present on the surface of bacteria inhabiting intestinal lumen, as has been mentioned above.

The phenomenon of protein co-aggregation in composition of amyloid aggregates has been demonstrated for numerous cases, number of which continues to increase [178]. The pair of proteins Rip1 and Rip3 could serve as an example of functional co-aggregation of proteins in compositions of amyloids. Their aggregation is one of the signals for necrolysis initiation [179], moreover, 3D-structure of heterofibrils of these proteins has been obtained [180]. The key role in this process belongs to the receptor-interacting protein kinase (RIP) homotypic interaction amino acid motifs (RHIM), which were also found in the Het-s protein (*Podospora anserina*) capable of forming amyloid aggregates [181]. Moreover, numerous examples of protein co-aggregation associated with different human amyloids are known, in particular, co-aggregation of the following proteins has been demonstrated: Aβ and Tau [182]; Aβ and amylin [183]; Aβ and PrP [184, 185].

There are evidences in the literature on co-aggregation of αSyn with different human proteins. Its aggregation could be induced *in vitro* by the Aβ fibrils (1-40 and 1-42) [186], IAPP [187], lysozyme, as well as GroES [188]. αSyn and Aβ physically interact in the patients with PD and AD [189]. It has also been demonstrated recently that αSyn co-aggregate with the NOS1AP protein [190].

The data have been accumulated recently that the proteins from other organisms could stimulate αSyn aggregation. Peptides of the PSMαs protein, which forms amyloid-like aggregates in *Staphylococcus aureus*, are capable of accelerating αSyn aggregation *in vitro* [191]. The similar effect was demonstrated for the SARS-CoV-2 N-protein [192], but no information on its amyloid properties is available. The most investigated example of interactions of amyloids from different organisms is the pair of proteins CsgA and aSyn. CsgA is the main component of extracellular fibrils, named curli, in *E. coli* and other bacteria [24, 193]. The results reported in two recent studies with model animals indicate that curli stimulate αSyn aggregation and development of synucleinopathies [194, 195]. Investigations were conducted with the rats prone to synucleinopathy development [194], or mice lacking microbiota and with enhanced production of αSyn [195]. In the course of experiments animals were perorally infected with *E. coli* strains containing curli, which resulted in the development of synucleinopathy. This was not observed in the animals from the control group infected with bacteria without aggregates. In the rats, an increase of the number of αSyn plaques in the intestine ganglion cells (Auerbach's plexus and submucosa) as well as in the hippocampus striatum neurons was observed. The authors also detected development of the innate immunity response in the brain. In the process, the experimental group of animals did not differ from the control group in weight, as well as in the level of cellular inflammatory processes in the mouth tissues, kidneys, eyes, and stomach [194]. It was shown in experiments with mice that only administration of bacteria containing curli causes impairment of motor functions and increase of the amount of aggregated and phosphorylated αSyn (S129) in various parts of the brain, as well as development of inflammatory processes in GIT and NS. In the *in vitro* experiments CsgA of *E. coli* and its orthologs from other organisms accelerate aggregation of αSyn [195, 196]. Although the question of the role of amyloid aggregates of CsgA in this process remains unresolved so far. Bacteria that produce non-amyloidogenic variant of CsgA, termed "SlowGo" cause the described symptoms less often [195]. Injection of the amyloidogenic CsgA peptides into the intestine wall of model mice results in the impairment of motor functions, as well as accelerates αSyn aggregation. These effects were not observed in the experiments with non-amyloid CsgA peptides [195]. On the other hand, there are indications that the slowed down aggregation of CsgA leads to acceleration of αSyn aggregation, i.e., it is the monomeric CsgA that plays a key role [196].

Accelerated aggregation of αSyn fused with yellow fluorescent protein (YFP) was observed in the *Caenorhabditis elegans* nematodes, which were fed with bacteria containing curli [194, 197]. In the process, the αSyn aggregation in nematodes correlated with the amount of curli, and colocalization of αSyn and CsgA in the muscles and neurons was observed [198]. And, finally, the genes *csgA* and *csgB* were identified in the screening aiming at identification of bacterial genes responsible for neurodegeneration in *C. elegans* producing αSyn (A53T) prone to aggregation. These nematodes exhibited degeneration of motor neurons and characteristic disruptions of behavior, when they were fed with *E. coli* K-12 bacteria normally producing curli. In the course of screening, derivatives of this strain were also analyzed with deletions of the non-essential genes. It was found out that the absence of exactly CsgA and CsgB in the bacterial cells facilitated decrease of pathogenesis in nematodes. Altogether 38 genes have been identified in the screening with the similar effects [198].

Potential role of CsgA in the development of PD in humans has been suggested by the recent clinical data. Proteins reacting with the antibodies against the CsgA peptide were found in the blood of patients with PD [199]. Moreover, it has been demonstrated recently that that the enteroendocrine cells, components of the intestine epithelium and, hence, are in direct contact with microbiota, produce αSyn [200, 201].

CONCLUSIONS

According to the most popular theory, development of PD begins in the gastrointestinal tract under the effect of external factors [54, 202]. Nevertheless, what exactly facilitates αSyn aggregation in ENS, and what molecular mechanisms underlie these processes remain unclear.

Currently numerous associations between the disbalance in gut microbiota and development of PD and other synucleinopathies have been described. In the presented review we attempted to summarize the most significant and relevant information on this topic. Several hypotheses have been suggested explaining how bacteria could cause development of synucleinopathies (Fig. 2). One of the most popular is the hypothesis associated with development of inflammation, which, in turn, causes aggregation of αSyn. This hypothesis is supported by the existence of positive correlation between the degree of inflammation caused by viral infection and amount of αSyn in the axons of gut neuron [65]. Although, even in this case, this association could be explained by different molecular mechanisms. The most plausible mechanism involves overproduction of αSyn during inflammation as well as its nitration [29, 165, 167]. On the other hand, there are a number of suggestions on the role of bacterial proteins or their metabolites in the development of synucleinopathies.

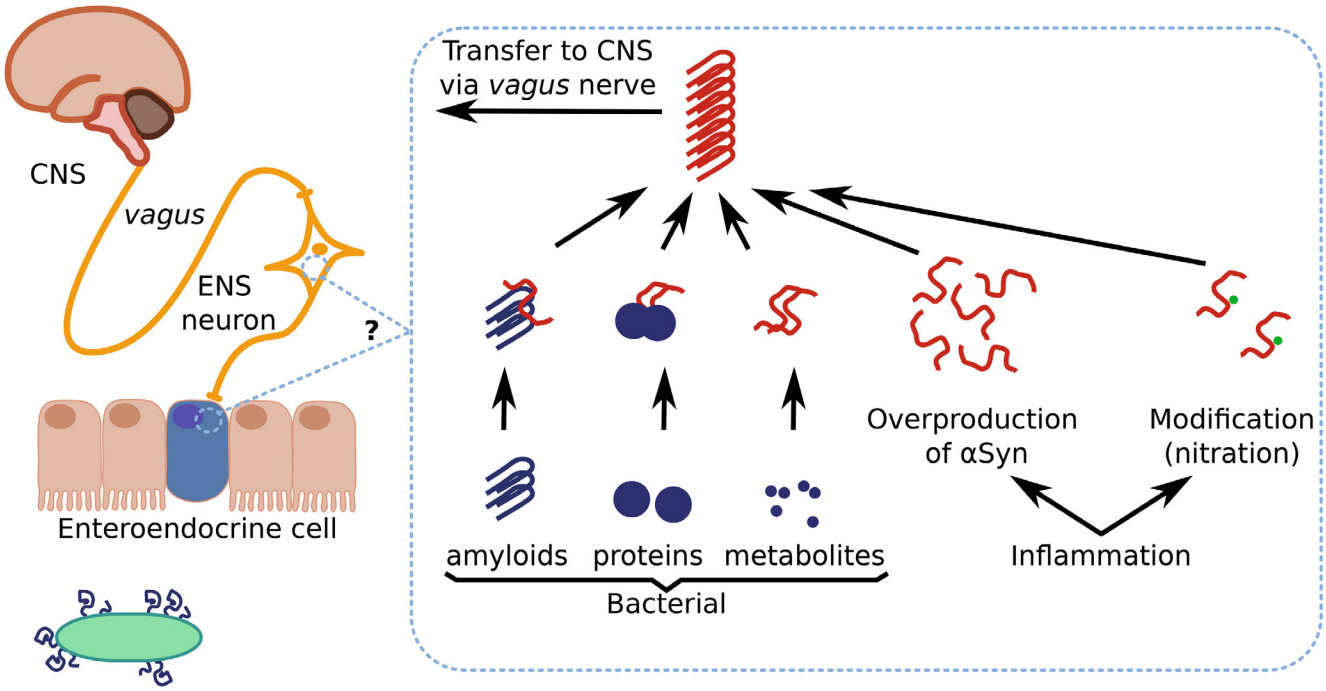

Fig. 2. Possible mechanisms of αSyn aggregation in the gut. Question mark indicated the fact that there are no exact data on the type of cells in which the processes presented in the inset occur.

Amyloid proteins from bacteria are the newest candidates for the role of the triggers of αSyn aggregation (Fig. 2). A whole range of studies discussed above supports this idea and demonstrates induction of αSyn aggregation by the CsgA fibrils [194-196, 198]. Similar effect could be promoted by the bacterial chaperons [42, 43]. Finally, PD development could be caused by bacteria metabolites (such as SCFAs) (Fig. 2), however, particular molecular mechanisms of this process, contrary to the previous cases, are not known yet. Existence of a barrier function in the gut epithelium is one of the counterarguments against the hypothesis of induction of αSyn aggregation by the factors of bacterial origin. However, its efficiency decreases significantly with aging, and permeability of the barrier for large molecules increases [154, 203, 204].

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