

Opinion

The microbiome, microbial-generated proinflammatory neurotoxins, and Alzheimer's disease

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1. Overview

Genomic sequencing studies indicate that the human gastrointestinal (GI) tract is a dynamic repository of about $\sim 10^{14}$ micro-organisms that outnumber host cells by at least 100 to 1.^{1–6} Collectively, these $\sim 10^{14}$ microbes contain about 10^{17} genes; the number of microbial genes is at least 150-fold greater than the total number of human genes.^{3,6–10} About 98% of the microbiota in the human GI tract consists of anaerobic bacteria, with archaeobacteria, fungi, protozoa, prions, viruses of plant and animal origin, viroids and other micro-organisms, and other free nucleic acids, such as microRNAs, making up the remainder. Why evolution selected just 2 of the 54 recognized major divisions of bacteria *Bacteroidetes* and *Firmicutes* to populate the human GI tract is both enigmatic and open to speculation—these 2 major phyla represent the “bacterial core” of our microbiome. The ability of *Bacteroidetes* and *Firmicutes* to coexist symbiotically, to generate essential vitamins and cofactors, and to process dietary constituents such as fiber may have made them particularly suitable to support human immunity, physiology, biochemistry, and neurochemistry.^{3,9–12} Of these 2 phyla, the *Bacteroidetes*, the largest class of obligate anaerobic gram-negative (G⁻) bacteria of the human GI tract, release extraordinarily complex mixtures of amyloids, lipopolysaccharides (LPSs), enterotoxins, and neurotoxins. Microbiome-derived exudates appear to be noxious to multiple aspects of microbiome–host interactions, including (1) GI tract and blood–brain barrier structure and integrity; (2) systemic, central nervous system (CNS), and peripheral nervous system (PNS) homeostasis and equilibrium; and (3) progressive inflammatory degeneration within the human nervous system. Interestingly, unique LPS toxins of the microbiome-abundant *Bacteroides fragilis* (BF-LPS) and the *B. fragilis* toxin (BFT) fragilysin are among the most barrier-disruptive and proinflammatory neurotoxins known.

This paper overviews some current research and emerging concepts published over the past 6 months on (1) the toxic array of substances generated by *B. fragilis*; (2) the potential contribution of microbiome-generated factors such as BF-LPS in driving proinflammatory signaling both systemically and within the nervous system; and (3) the recent recognition of the beneficial effects of dietary fiber on the growth and proliferation of *B. fragilis* and other prolific microbial species in the human GI tract microbiome, with specific reference to Alzheimer's disease (AD) neuropathology wherever possible.

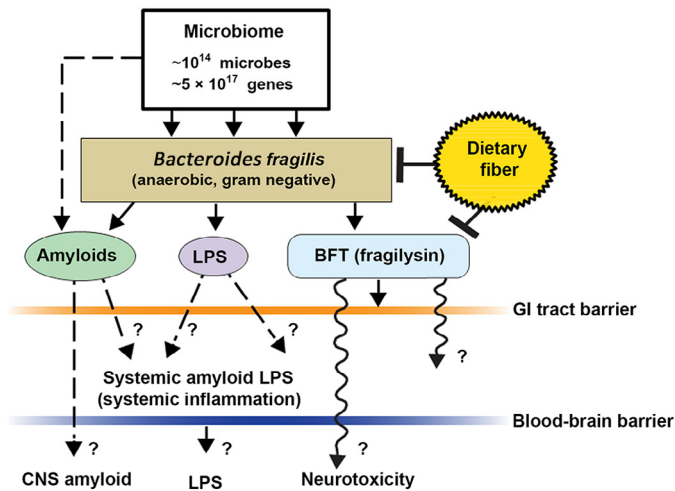
2. BF-LPS amyloids, LPSs, and enterotoxins

A priori, we would like to note that in this paper we are using as the principal illustration a major anaerobic microbial species of the GI tract, *B. fragilis*, as a prime example of an abundant, G⁻ bacteria of the microbiome; it should be kept in mind that at least 1000 additional species of GI tract bacteria have both a dynamic and opportunistic potential to similarly contribute to (1) the homeostatic maintenance of the GI tract–CNS axis in health and (2) the development of both systemic and inflammatory neurodegenerative disease (Fig. 1). First, *B. fragilis* produces 3 major classes of toxic secretory products: amyloid, LPS, and enterotoxins. They are briefly defined here.

1. *Amyloid*. The term *amyloid* is generic for any insoluble, lipoprotein-enriched molecule exhibiting β -pleated sheet structures oriented perpendicular to its fibrillar axis; a remarkably wide variety of microbiome-resident species, particularly bacteria and fungi, generate significant quantities of functional amyloids and related microbial exudates.^{6–10} Interestingly, well over half of all known proteins contain “unstructured” regions of amino acids that are intrinsically amyloidogenic.^{7–11} For example, the amyloids that characterize AD consist largely of “perivascular” amyloid deposits enriched in the 40-amino acid A β 40 peptide; “parenchymal” amyloid, enriched in the 42-amino acid A β 42 peptide; and “nuclear” amyloids, which contain highly complex mixtures of lipoprotein fibrils and dense amyloid aggregates.^{9–12} Interestingly,

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Inflammatory neurodegeneration (CNS inflammation and immune deficits)

Fig. 1. Schematic representation of the potential contribution of gastrointestinal (GI) tract microbiome-derived amyloids, lipopolysaccharides (LPS), and endotoxins to systemic inflammation and/or to central nervous system (CNS) neurotoxicity and immune deficits. One of the major microbial species in the human GI tract is *Bacteroides fragilis*. In concert with other microbiome components, this anaerobic gram-negative bacillus generates complex mixtures of amyloid, LPS, and/or potent neurotoxins such as *B. fragilis* toxin (BFT; fragilysin), one of the most potent proinflammatory molecules known.^{20–23} Fragilysin is recognized to both (1) increase the paracellular permeability of the intestinal epithelium largely via the dissolution of tight junctions in epithelial cells^{16–19} and (2) at low, physiologically realistic (nanomolar) concentrations, induce robust inflammatory signaling (such as activation of nuclear factor kappa B (NF- κ B)-DNA binding) in human brain cells in primary culture^{20–24} (unpublished observations). The presence of *B. fragilis* and/or *B. fragilis*-derived amyloids, LPSs, or endotoxins such as BFT in the bloodstream during systemic inflammation (bacteremia) is more common than any for any other anaerobe of the microbiome.^{15–23} In combination with other facultative/obligate anaerobic microbes, their secretory exudates are extremely powerful proinflammatory and innate immune system activators in the CNS once they pass GI tract and blood–brain barriers. These actions would further induce vascular permeability, trigger host immunogenicity, and induce the generation of reactive oxygen species and NF- κ B signaling. For example, (1) these neuropathogenic signals further promote amyloid aggregation and inflammatory degeneration characteristic of age-related neurologic diseases such as AD and other neurologic disorders that exhibit defective A β 42 peptide clearance mechanisms and progressive amyloidogenesis,^{9,24,25} and (2) *B. fragilis*-derived toxins are also responsible for the majority of localized abscesses within the cranium.^{24,25} As a major component of the human microbiome, GI tract microbial sources of amyloid, LPS, and/or other microbial-derived endotoxins have a remarkable potential to contribute to both systemic amyloid and CNS amyloid burden in their respective CNS compartments. This contribution of noxious, proinflammatory molecules from the GI tract microbiome may be increasingly important during the course of aging, when both the GI tract and blood–brain barriers become significantly more permeable.^{14–23} Interestingly, high intake of dietary fiber is a strong inhibitor of *B. fragilis* abundance and proliferation in the human GI tract and as such is a potent inhibitor of the neurotoxic *B. fragilis*-derived amyloids, LPSs, and enterotoxins. Hence dietary fiber-mediated suppression of *B. fragilis* abundance may be beneficial for both human GI tract and CNS health.^{14,21–26}

common tertiary protein structures or pathogenic-associated molecular patterns between microbial and host amyloids (1) may be involved in propagation or acceleration of amyloidogenesis through “molecular mimicry”

and (2) may be important in the priming of the host innate immune system and/or microglial cell activation by microbiota, a factor that may enhance inflammatory and immunologic responses to AD amyloid.^{9–16}

2. *LPS*. Distinguishing components of the outer leaflet of the outer membrane of G⁻ bacteria shed into the extracellular space, LPSs have historically been thought to play some host-pathogen immune-evasion strategy useful to bacterial survival while eliciting strong immune and proinflammatory responses within the host.^{8,10,17–20} Although LPSs contain large and hypervariable polysaccharide/oligosaccharide regions, a relatively conserved lipid region (known as the “lipid A” core) is the endotoxic and biologically active moiety that is responsible for the induction of systemic inflammation and ensuing septic shock.^{9–12,14–18} Interestingly, it has been recently shown by several independent groups that (1) LPS strongly promotes amyloid aggregation,^{9,10,20} and (2) BF-LPS is one of the most potent inducers of nuclear factor kappa B (NF- κ B) activation in primary human neuronal-glia cocultures known.^{17–20}
3. *Enterotoxins: fragilysin*. This is also known as BFT, a Zn²⁺-requiring metalloprotease highly cytopathic to intestinal epithelial cells with the following characteristics: (1) possesses broad proteolytic specificity of hydrolytic cleavage adjacent to leucines;^{17–19} (2) hydrolyzes gelatin, fibrinogen, and extracellular matrix proteins such as the extracellular domain of type 1 transmembrane proteins such as E-cadherin;^{15,19} (3) rapidly degrades intracellular proteins such as actin and myosin;^{15,16,20} and (4) disrupts the tight-junction zona occludens-1 protein of the intestinal epithelial cell.^{16–21} Taken together, these recent findings indicate that fragilysin’s pathogenic actions (1) interrupt the integrity of intercellular adhesion;^{15,18,19} (2) increase mucosal permeability and the permeability of the intestinal epithelium to GI tract contents;^{14–17} and (3) induce epithelial cell–cell detachment, laying the morphologic basis for a compromised and “leaky” GI tract barrier.^{17–23}

Clinically, the presence of BF-LPS in the blood serum signifies (1) a breach of epithelial cell–GI tract barriers; (2) an early, major, and contributing factor to the initiation and propagation of systemic inflammatory disease; and (3) the first major biophysical barrier crossed for complex mixtures of proinflammatory toxins of the GI tract contents to gain access to the systemic circulation, and onward to the blood–brain barrier of the CNS. It would be surprising if BF-LPS were not similarly effective in weakening tight junctions of the blood–brain barrier, and recent data support this concept.^{17,19,20} Furthermore, in primary human neuronal-glia cocultures BF-LPS is (1) an unusually potent inducer of the proinflammatory transcription factor NF- κ B (p50/p65 complex) and hence proinflammatory gene expression programs and (2) recognized by toll-like receptors 2 and 4 (TLR2, TLR4) and/or cluster of differentiation 14 (CD14) microglial cell receptors, as are the amyloid peptides that characterize AD neuropathology.^{9,10,20}

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