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Pro-Inflammatory Neurotoxins Derived from the Gastrointestinal Tract Microbiome in Alzheimer's disease

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The microbiome of the human gastrointestinal tract is a very complex and dynamic internal prokaryotic ecology with incredible variety, diversification, and complexity. This dynamic repository of microorganisms has the world's biggest interactive source and greatest density of bacteria, together forming the world's largest 'diffuse organ system' that is at least as metabolically active as the liver. This microbiome has a significant impact on the health, wellbeing, and vitality of the human host via the extracellular fluid (ECF), cerebrospinal fluid (CSF), lymphatic and glymphatic circulation, endocrine, systemic, and neurovascular circulation, and/or the central and peripheral nervous systems (CNS, PNS). The Human Microbiome Initiative (HMI) and the Unified Human Gastrointestinal Genome (UHGG) consortium recently classified over 200 thousand diverse, non-redundant prokaryotic genomes in the human GI-tract microbiome, involving approximately 5,000 different GI-tract microbes that encode nearly 200 million different protein sequences. While the majority of microbiome-derived proteins, lipoproteins, and nucleic acids provide essential microorganism-specific gene products for microbial structure, function, and viability, many of these components are also shed from Gram-negative bacterial species' outer cell walls into surrounding biofluids and/or the systemic circulation. Several of the microbial-derived species produced by GI-tract microorganisms are among the most proinflammatory and neurotoxic substances known, and these secreted neurotoxins disrupt cell-cell adhesion and easily translocate through plasma membranes into the systemic circulation, brain, CNS, and PNS. Many independent research groups have discovered microbial proteins such as Gram-negative bacteria-derived lipopolysaccharide (LPS), bacterial amyloids, and more recently small non-coding RNA (sncRNA) microbial-derived neurotoxins within the brain cells and CNS tissues of Alzheimer's disease patients (AD). This 'Commentary' will highlight the most recent findings on these microbially derived secreted toxins, their neurotropic properties, and the potential contribution of these neurotoxic and pro-inflammatory microbial exudates to age-related inflammatory neurodegeneration, with specific reference to the human GI-tract abundant Gram-negative anaerobe Bacteroides fragilis and to Alzheimer's disease whenever possible.

OVERVIEW OF HUMAN MICROBIOME

The human microbiome, which is found in all higher eukaryotes, is a highly dynamic and interacting community of microorganisms made up mostly of aerobic and anaerobic bacteria, archaebacteria, fungi, protozoa, viruses, and other microbes. The human microbiome makes up a large part of the human 'meta organism,' and it provides significant commensal and/or symbiotic benefit to the human host. The human microbiome is dominated by aerobic and anaerobic Gram-positive and Gram-negative bacteria of the gastrointestinal (GI) tract, and the influence of microbial secretions on human brain health and illness is becoming increasingly acknowledged. Bacteroidetes, the largest phylum of anaerobic Gram-negative bacteria in the GI-tract microbiome, have the potential to secrete a remarkably complex array of pro-inflammatory neurotoxins, including microbial surface lipopolysaccharide (LPS), highly immunogenic bacterial amyloids, and proteolytic peptides, while generally beneficial to the host when confined to the interior of the GI-tract (sncRNA). As the GI-tract and blood-brain barriers (BBB) become altered, leaky, and/or dysfunctional in their permeability with ageing and disease, including primarily gastrointestinal, systemic vascular, and neurovascular disease, the deleterious neurotoxic effects of these bacterial exudates become more significant. Approximately 99.5% of all resident microorganisms in the human GI-tract microbiome are facultative and/or obligate anaerobic bacteria from just two major bacterial divisions, Firmicutes and Bacteroides, which comprise the human GI-tract microbiome's "bacterial core." Microbes in the deeper and more anaerobic regions of the small intestine are the most enriched in obligate anaerobic microbial species. The 3.5 cm diameter, 7 m long human GI-tract varies in pH and oxygen availability along its length; microbes in the deeper and more anaerobic regions of the small intestine are the most enriched in obligate anaerobic microbial species. The phylum Bacteriodetes is the most prevalent Gram-negative bacteria in deep GI-tract areas, with the obligatory Gram-negative anaerobe, nonspore producing bacillus Bacteroides fragilis being a significant genus-species.