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THE INTESTINAL ECOSYSTEM IN NEUROINFLAMMATION AND NEUROPROTECTION: MECHANISTIC INSIGHTS AND EMERGING EVIDENCE WITH RECENT ADVANCEMENTS

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ABSTRACT

The intestinal ecosystem (gut microbiota, intestinal mucosa, intestinal immune cells, neuronal components (enteric nervous system and vagus nerve), and metabolic products of microbes) has a potent influence on homeostasis of the central nervous system (CNS). The mounting preclinical and clinical evidence is pointing towards the involvement of gut-derived signals in both neuroinflammatorysignaling and neuroprotectivesignaling to exacerbate neurological disease and maintain neuronal activity respectively. It is a survey of mechanistic knowledge (barrier integrity, immune modulation, microbial metabolites, vagal and enteric signaling), clinical and experimental evidence on large-scale disorders (Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, autism spectrum disorder), and new ways of therapeutic intervention (dietary modulation, psychobiotics, fecal microbiota transplantation, metabolites and receptor-targeted drugs, and neuromodulation). We present unanswered questions and give a roadmap of a translational research and clinical trials to implement the intestinal environment to shield the brain.

KEYWORDS: Intestinal Ecosystem, Neuroinflammation and Neuroprotection.

INTRODUCTION[1-3]

The importance of the gut to the brain (humanized)and envision the gut as a noisy gossipy neighborhood: trillions of microbes produce signals, metabolites and immune signals which the brain perceives in an unending stream. In the past decade, animal experimental projects and rising human evidence have produced a microbiota-gut-brain axis - a bi-directional line of communication of immune and neural (vagus and enteric nervous system), endocrine and metabolic pathways. This axis may be used to promote or support neuroprotection and recovery or neuroinflammation and disease progression using microbial composition, barrier health, diet, infections, and host genetics. The idea of the gut being able to regulate the development of microglia, the blood-brain barrier (BBB) and neuroimmune condition has no longer remained an inflammatory one.. (PubMed)Pathways through which the intestinal ecosystem is connected to neuroinflammation and neuroprotection are mechanical.

obstruction role: gut permeability - systemic inflammation – brain Failure of the intestinal barrier (mucus, epithelial tight junctions, and immune surveillance) can lead to the entry of microbial products (lipopolysaccharide [LPS]) and peptidoglycan into the circulation, causing systemic activation of the innate immune. This would be non-infectious systemic inflammation that could predispose to BBB perturbation and microglia stimulation and seed chronic disease neuroinflammation. Conversely, the barrier integrity (diet, specific probiotics or tight junction-stabilizing intervention) reduces peripheral inflammation and is associated with an improved neurodegenerative model outcome. (MDPI)Metabolites of microbes - short-chain fatty acids (SCFA), bile acids, tryptophan metabolites.

The key concentrators include microbial metabolites[4,5]

SCFAs (acetate, propionate, butyrate) control immune cells, microglia maturation and activity, epigenetics (histone deacetylase inhibition), as well as immunoregulatory and neuroprotective effects in most preclinical models. SCFA profiles are altered with the diseases. (PMC)Tryptophan-kynurenine metabolite neuroinflammatory-tone/ excitotoxicity dependence and microbial regulation of serotonin precursors. MMBA and other microbial-derived micro-molecules act in receptors of bile acid or other micro-molecules, adjusting microglia and peripheral immune cells. (PMC)

Immune regulation: natural and adaptive defences[6]

It has been proposed that intestinal microbes condition the systemic immune system: certain of the taxa train regulatory T cells (Tregs) and anti-inflammatory cytokines whereas others

train proinflammatory Th17 or monocyte cells. Systemic immune modulations affect CNS immunity (activation of microglia, responses of astrocytes) and can tip the scale towards either neuroinflammation or neuroprotection. This axis is based on the interaction of the signaling of the pattern-recognition receptor (TLRs, NLRs) and the activation of the inflammasome and ligands of the every microbe.

Neural pathways: vagus nerve and enteric nervous system (ENS)[7]

A direct high-speed pathway operated by the vagus nerve: the metabolites of microbes, enteroendocrine products and vagal afferent stimulation alter the mood, autonomic control and neuroimmune control areas of the brain. Systemic inflammation (the cholinergic anti-inflammatory pathway) can be suppressed by vagal signaling, in addition to indirectly affecting the state of microglia. ENS reorganization is also capable of modifying motility and secretion, providing additional control over microbial composition –a feed back. (ScienceDirect)

Effectors Microglia and glia

The microglial responses and development are microbial cued. The rodents that are germ-free have immature microglia which reacts abnormally to insults; the recovery of microglial maturation can be achieved by recolonization or supplementing SCFA, which connects the microbiota directly to CNS innate immunity. Neuroinflammatory regulation also involves astrocyte modulation due to microbial metabolites (e.g. aryl hydrocarbon receptor ligands). (PMC).

Neurological disorders Evidence (selected highlights)[8-12]

Alzheimer's disease (AD)

Various groups of evidence have indicated that gut dysbiosis is associated with heightened systemic inflammation, dysregulated metabolic events and enhanced amyloid/tau pathology in animal models; human experiments have revealed that in AD and mild cognitive impairment, there are specific microbiome footprint signatures. Certain combinations of probiotic treatment and dietary intervention decrease inflammatory biomarkers and demonstrate slight signs of cognition in small studies - encouraging but not conclusive. (PMC).

Parkinson's disease (PD)

Motor symptoms may be preceded by constipation, enteric alpha-synuclein pathology. The changes in gut microbiota (a decrease in the number of SCFA generators, an increase in the number of proinflammatory taxa) have been repeatedly found in the PD cohorts. The results of early clinical trials and pilot randomized studies of fecal microbiota transplantation (FMT) indicate that the treatment is safe and variably effective: some trials have found a symptomatic benefit (particularly against constipation and nonmotor symptoms) and larger randomized controlled trials have found little motor benefit so far. The complexities noted in these mixed clinical outcomes include the selection of donors, dose, route and patient heterogeneity are important. (JAMA Network).

Multiple sclerosis (MS)

In preclinical models, Th17/Treg balancing has been demonstrated to affect susceptibility and severity of autoimmune demyelination through the effects of particular gut bacteria. It is shown that microbiome shifts occur in MS patients, and the intervention with dietary and probiotics as early-phase intervention is the use of probiotics to regulate the tone of the immune system. (Frontiers).

Stroke and ischemia

Post stroke gut dysbiosis has the potential to increase systemic inflammation and secondary brain injury whereas the size of infarcts and functional recovery in response to manipulation of microbiota have been observed to vary in animal models. Gut-directed therapies to improve post-stroke outcomes are becoming popular. (MDPI).

Psychiatric disorders and neuro developmental disorders

There is some evidence that the microbiota composition in the early stages of life is associated with neurodevelopment and susceptibility to autism spectrum disorder (ASD) and stress/anxiety/depression. Mechanisms are immune priming, modified tryptophan metabolism as well as, microbial metabolites that influence synaptic development. (PubMed) Meanings of therapy and translational progress.

Diet and prebiotics

Dietary fiber enhances the production of SCFAs and tends to protect the integrity of the barrier and anti-inflammatory cues. Accurate nutritional interventions (Mediterranean, high-fiber) are under testing in terms of cognitive and motor results. (PMC)

Probiotics, psychobiotics, postbiotics

Certain probiotic strains and specific microbial products (postbiotics) demonstrate positive effects in animal models and small benefits in limited clinical trial in humans regarding cognition and mood. Nonetheless, interpretation is complicated by heterogeneity in strains, dosing and endpoints. Large powerfully powered RCTs are underway. (Frontiers).

Fecal Microbiota Transplantation (FMT)

FMT has strong outcomes in C. difficile infection and clinical trials are in PD, AD, and other disorders. Safety seems to be okay in regulated conditions but efficacy seems to be changeable- depending on the microbiota of the donor, recipient baselines, and delivery route. There are core neurological neutral, but nonmotor symptom and GI signals, in some randomized trials. (JAMA Network).

Molecules and receptor targets of microbes

Specific interventions (e.g., the use of target host receptors to microbial metabolites, such as SCFA receptors, aryl hydrocarbon receptor) or precise assembly of defined interventions can be achieved using other means than live microbes. The preclinical results are encouraging; human translation is still being undertaken. (Exploration Publishing).

Vagal stimulation & Neuromodulation

Systemic inflammation can be tamed with bioelectronic modulation of the vagus nerve and is a promising complement to microbiome therapy. This strategy finds support in preclinical and clinical efforts in the area of inflammatory diseases; active research is in progress to apply it to neurodegenerative diseases. (Taylor & Francis Online) Difficulties, constraints and unresolved issues.

Causality and confounding

The human microbiome research is frequently cross-sectional; it is hard to separate the cause and consequence. The methods will need longitudinal cohorts and Mendelian randomization. (Annual Reviews).

Heterogeneity

The variations in microbiome composition, genetics, diet, drug use (particularly antibiotics and proton pump inhibitors), and geography make people heterogeneous and thus difficult to replicate.Standardization of intervention Probiotics, FMT (donnae selection, processing) and

metabolite dosing do not have standardized procedures of neurological outcomes. (Springer Link).

Mechanistic depth: It takes integrated multi-omic and mechanistic-humanized analyses to translate metabolites and immune signatures into validated biomarkers and therapeutic targets. (PMC).

Future trends and suggestions[13,14]

Combination of metagenomics, metabolomics, immune profiling, neuroimaging, and clinical measures using integrative longitudinal human cohorts is needed to trace gut perturbation/neuroinflammation maps. (Frontiers).

Precision interventions: donor selection algorithms of FMT, strain-level probiotic-therapy, small molecules that target a specific host receptor all deserve the priority over general strategies. (Nature).

Mechanism-based trials: minor adaptive RCT utilizing mechanistic biomarkers (SCFAs, cytokines, microglial PET imaging) will allow learning faster and quicken the disposal of big trials.Safety plans: long-term follow-up of interventions that alter immune tone is important especially with autoimmune or immunocompromised diseases. (JAMA Network).

CONCLUSION

The intestinal ecosystem is a flexible node, which influences neuroinflammatory and neuroprotective outcomes throughout the lifespan. Although there are exciting translational opportunities, including diet and psychobiotics, FMT and receptor-targeted therapeutics, clinical upgrades need serious, mechanically informed clinical trials and regulated interventions. The combination of systems biology, clinical neurology, and precise microbiome therapeutics will make the field transform gut-brain knowledge into valuable neuroprotective approaches.

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