Commentary

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A gut feeling about stroke reveals gut-brain axis' active role in homeostasis and dysbiosis

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Abstract

Peripheral inflammatory responses accompany many neurological disorders, including stroke. The gut-brain axis opens new avenues in our understanding of stroke progression and abrogation of secondary cell death. Certain microbiomes, especially those related to inflammation, appear to closely reflect the homeostasis and dysbiosis of both the brain and the gut, suggesting their potential application as biomarkers and therapeutic targets. A paradigm shift from purely central towards incorporating peripheral sequestration of cell death pathways may improve stroke therapeutic outcomes. Recognizing this gut-brain axis as key to disease pathology and treatment is likely to usher innovative approaches in cell-based regenerative medicine for stroke.

Keywords

Cerebral ischemia, gastrointestinal tract, central nervous system, peripheral nervous system, inflammation, microbiome, stem cells

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Stroke is a primary cause of death and disability in the United States and worldwide but has limited effective treatment; thus, it remains a significant unmet clinical need that warrants novel therapy. Whereas the primary insult may not be rescued, the secondary cell death presents as a viable stroke therapeutic target. Understanding the cell death mechanisms accompanying stroke progression will not only provide insights into finding sensitive biomarkers of disease pathology but also guide the development of novel strategies designed to retard this stroke-induced secondary cell death. Because many stroke survivors are left with disabling motor and cognitive impairments which are exacerbated by secondary cell death, abrogation of this progressive cell death will likely improve the quality of life of stroke patients.

Because of the well-established brain pathology of stroke, research efforts to reveal the underlying mechanisms of stroke progression have largely probed the central nervous system (CNS). Accumulating evidence now implicates the critical participation of the peripheral nervous system in the secondary cell death of stroke, in particular, the gut-brain axis closely approximates stroke progression.[1–3] Key to this pathological link is the aberrant elevated inflammation in both the gut and brain after stroke. A healthy gut manifests a highly diverse microbiome, which in humans may consist of 10–100 trillions of microorganisms and bacteria, whereas a pathologic gut displays a limited and distinct set of inflammation-relevant microbiomes. Mechanisms linked to gut dysbiosis, such as skewed metabolic profiles, dysregulated immune systems, and direct translocation of gut microbiomes to pathologic organs, provide a putative biological mechanism by

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which the brain may communicate with the gut and vice versa during stroke progression.

The enteric nervous system functions autonomously, but the process of digestion requires a coordinated regulatory control involving parasympathetic and sympathetic fibers that link the CNS with either the enteric nervous system or the digestive tract. These fiber formations connecting the gut and the brain allow the gut to communicate sensory information to the CNS; similarly, these connections aid in CNS regulation of gastrointestinal (GI) function. This gut-brain axis represents the physiological framework for the maintenance of homeostasis with the CNS and GI tract working together towards this important cell, tissue, organ, and organism survival function. Following a CNS insult, including stroke, the same gut-brain axis normally employed for homeostatic regulation is also mobilized to control dysbiosis.[4] That a signature inflammation profile of the gut microbiome may be mirrored in the brain microbiome, specifically in the ischemic penumbra, represents an innovative research endeavor towards our understanding of stroke pathology and its treatment. Unique microbiomes exist beyond the gut and brain, and have been well characterized in the vagina, oral cavity, and skin, which may influence stroke outcomes.

This paradigm shift of thinking outside the brain and pursuing a holistic approach in treating stroke and other neurological disorders has recently been embraced by the stem cell-based regenerative medicine field. Cell transplantation, along with the delivery of cell-derived exosomes, microvesicles, microRNAs, and trophic factors, among others, has expanded the stroke therapeutic targets from central to peripheral organs.[5,6] Profiling of unique microbiomes in the brain and gut (as well as other peripheral organs) via single-cell omics and transcriptomics[7,8] will be instrumental in understanding the pathology and developing treatment strategies such as cell-based regenerative medicine for stroke and other neurological disorders.[5]

Our recent studies in experimental Parkinson's disease (PD) reveal the critical role of the microbiome as a biomarker and therapeutic target.[9,10] The prevailing dogma in PD is its overarching classification as a brain disorder with the depletion of nigrostriatal dopamine as its key pathology; thus, its diagnosis and treatment have mainly focused on addressing this brain manifestation. A paradigm shift implicates the periphery as PD's origin. Indeed, gut dysbiosis precedes brain pathology, with abnormal GI functions predating the hallmark motor symptoms of PD.[9,10] Cognizant of this gut-to-brain disease propagation, probing the gut microbiome should reveal innovative insights into PD pathology and its treatment. Targeting PD at its peripheral origin may allow a disease-modifying outcome instead of the current palliative relief. Our two recent studies identified three key gut microbiota (LAB158, BAC303, and EREC482), which are upregulated after neurotoxin lesions, tightly associated spatially and temporally supporting the gut-to-brain evolution of pro-inflammation and neurotoxicity, and abrogated by stem cell treatment.[9,10] That gut inflammatory microbiomes may induce neurodegeneration in PD suggests that similar dysbiotic gut-brain axis can influence the inflammation-plagued secondary cell death in stroke. In-depth identification of specific microbiomes in both gut and brain may reveal the homeostatic microenvironment that harbors a healthy and neuroplastic brain, and the dysbiotic microenvironment that drives neuroregeneration. To this end, single-cell omics and intragut stem cell therapy represent as innovative tools in probing the gut-brain axis in stroke, PD, and other neurological disorders.

These pioneering reports directly implicate the key role of the gut microbiome in CNS disease pathology, and also provide evidence that targeting the gut and its inflammatory microbiome stands as a novel stroke therapy. Recognizing that the gut is a major source of inflammation and a key pathological contributor to stroke, it is appealing to pursue the logical transition of interrogating the gut, in addition to the brain, to fully understand stroke pathology and its treatment.

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References

1. Venkat P, Chen J and Chopp M. Exosome-mediated amplification of endogenous brain repair mechanisms and brain and systemic organ interaction in modulating neurological outcome after stroke. *J Cereb Blood Flow Metab* 2018; 38: 2165–2178.

2. Singh V, Sadler R, Heindl S, et al. The gut microbiome primes a cerebroprotective immune response after stroke. *J Cereb Blood Flow Metab* 2018; 38: 1293–1298.
3. Arumugam TV, Manzanero S, Furtado M, et al. An atypical role for the myeloid receptor Mincle in central nervous system injury. *J Cereb Blood Flow Metab* 2017; 37: 2098–2111.
4. Chi L, Du K, Liu D, et al. Electroacupuncture brain protection during ischemic stroke: a role for the parasympathetic nervous system. *J Cereb Blood Flow Metab* 2018; 38: 479–491.
5. Otero-Ortega L, Gómez de Frutos MC, Laso-García F, et al. Exosomes promote restoration after an experimental animal model of intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2018; 38: 767–779.
6. Sun P, Liu DZ, Jickling GC, et al. MicroRNA-based therapeutics in central nervous system injuries. *J Cereb Blood Flow Metab* 2018; 38: 1125–1148.
7. Thomson-Luque R, Wang C, Ntumngia FB, et al. In-depth phenotypic characterization of reticulocyte maturation using mass cytometry. *Blood Cells Mol Dis* 2018; 72: 22.
8. Cheemalapati SV, Winskas J, Wang H, et al. Subcellular and in-vivo nano-endoscopy. *Sci Rep* 2016; 6: 34400.
9. Lee JY, Tuazon JP, Ehrhart J, et al. Gutting the brain of inflammation: a key role of gut microbiome in human umbilical cord blood plasma therapy in Parkinson's disease model. *J Cell Mol Med* 2019; 23: 5466–5474.
10. Lee JY, Tuazon JP, Corey S, et al. A gutsy move for cell-based regenerative medicine in Parkinson's disease: targeting the gut microbiome to sequester inflammation and neurotoxicity. *Stem Cell Rev Rep* 2019; 15: 690–702.