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The Gut-Brain Axis: How the Microbiome may Influence Brain Tumors, A Narrative Review

Farajirad E[1], Tohidi H[2], Mohazzab Torabi S[3] and Farajirad M[3]*

[1]Division of Neurology, Department of Medicine, Toronto General Hospital, University of Toronto, Toronto, Canada

[2]Department of Medicine, Toronto General Hospital, University of Toronto, Toronto, Canada

[3]Department of Neurosurgery, Mashhad University of Medical Sciences, Iran

Review Article

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***Corresponding authors:** Mohammad Farajirad, Professor of Neurosurgery, Department of Neurosurgery, Mashhad University of Medical Sciences, Mashhad, Iran, Email: farajirad@yahoo.com

Abstract

Aim: To review the current literature and demonstrate the potential relationship between gut microbiome and brain tumor.

Methods: A comprehensive search of the available literature was conducted using the PubMed, Google Scholar, OVID, Embase and other database to identify studies investigating the relationship between the gut microbiome and brain cancer. The search was limited to articles published in English between 2010 and 2022.

Conclusion: While the research on the relationship between the gut microbiome and brain cancer is limited, the studies that have been conducted suggest that there may be a connection. The gut microbiome has been shown to play roles in a number of diseases, and some evidence suggests that it may also be involved in the development and progression of brain cancer. The gut microbiome may suggest a new method for the prevention, diagnosis, and treatment of brain cancer and further research in this area has the potential to lead to new and innovative strategies for managing this disease.

Keywords: Gut Microbiome; Brain Tumor; Central Nervous System

Introduction

The annual global age-standardized incidence and mortality rates of primary tumors in the central nervous system (CNS) are approximately 23.41 and 4.42 per 100,000, respectively [1]. Brain tumors can be classified based on their histological phenotypes, gene mutations, and molecular profiles Gittleman H, et al. [2] Studies have indicated that mutations targeting isocitrate dehydrogenase 1/2 (IDH 1/2) are linked to characteristic DNA methylation patterns [3,4]. The human gut is home to a diverse community of microorganisms, collectively referred to as the gut microbiome. This microbiome plays a crucial role in maintaining overall health and well-being, as it influences several physiological processes, including digestion, metabolism, and the immune system. In recent years, research has shown that the gut microbiome may also have a connection to brain health and disease, including brain cancer [5]. These long-distance interactions may occur due to the gut-brain axis, a complex and bidirectional communication system between the brain and the gut [6]. Few studies have delved into the connection between changes in gut microbiota and non-digestive cancers [7]. However, there may be interactions between intestinal microbiota and cancers located in different areas of the body due to neural, endocrine, or immune afferents. In other words, studies have shown that alterations in the gut microbiome can have a significant impact on the brain and nervous system, leading

to changes in behaviour, mood, and cognition [8,9]. These changes are thought to occur through several mechanisms, including the production of neurotransmitters and other signalling molecules, the modulation of the immune system, and the influence on systemic inflammation.

Additionally, the gut-brain axis is a two-way communication channel connecting the central nervous system and the gastrointestinal tract. It involves various elements such as the enteric nervous system, gastrointestinal microbiota, autonomic nervous system, neuroendocrine mediators, and the CNS, which together form a complex network that affects biological homeostasis [10]. Researchers have also explored the potential role of the gut microbiome in the development and progression of brain cancer [11]. There is evidence to suggest that the gut microbiome can influence the growth and spread of brain tumors by altering the local microenvironment and contributing to systemic inflammation [12]. Despite its potential significance, the gut-brain connection in the context of cancer has not been extensively investigated, despite the involvement of cytokines in the immune response. Thus, in following we will highlight narratively about conceivable causes those immune responses targeted towards cancer cells in the brain and it's affected by microbial community in the gut, or theories that changes in microbiota structure could lead to cancer proliferation.

Methods and Materials

A comprehensive search of the available literature was conducted using relevant databases such as Medline via Ovid SP, EM- BASE via Ovid SP, PubMed, Scopus, Pro Quest dissertations data- base, Open SIGLE, Grey Matters, and Google Scholar and Web of Science (WOS) were searched for inclusion of papers published in international journals. In the current review, an experienced clinical librarian afforded all parts of search protocol including compiling search strategy, running the strategy in different sources, and full text retrieval of papers. The search strategy for Medline via Ovid SP adjusted for other resources too. The priority of search strategy was to be as sensitive as possible. For inclusion of grey literature, Pro Quest dissertations database, Open SIGLE and Grey Matters, as well as Google Scholar were considered to provide a comprehensive collection of related papers. The search was limited to articles published in English between 2010 and 2022 and included keywords related to the gut microbiome and brain tumors, such as "gut microbiome," "intestinal flora," "brain tumors," and "glioma." The search results were screened for articles that were relevant to the research question and a selection of studies were included for review. The inclusion criteria were original research articles that investigated the relationship between the gut microbiome and brain tumors. Data Extraction: Data was extracted from the selected studies, including information on the study design, sample size, study population, and results. The extracted data was synthesized to identify patterns and trends in the research on the relationship between the gut microbiome and brain tumors. The quality of the selected studies was assessed using relevant quality assessment tools, such as the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials. The quality of the studies was used to inform the interpretation of the results and to assess the overall strength of the evidence. By conducting a comprehensive search of the available literature and applying rigorous selection and data extraction methods, this study aims to provide a comprehensive overview of the current state of the research on the relationship between the gut microbiome and brain tumors.

Discussion

The gut microbiome is a complex and dynamic community of microorganisms that reside in the human gut and play a crucial role in maintaining health and well-being. The gut hosts a remarkably diverse microbiota which can produce an extensive range of small molecules that influence several key pathways linked to immune balance and neurological function stability [13,14]. Recent researches have shed light on the impact of the gut microbiome on various physiological processes, including the brain and nervous system [15]. This has led to the exploration of the gut-brain axis, a complex and bidirectional communications network that influences behaviour, mood, and cognition through several mechanisms. Consequently, the study and control of the gut microbiota are emerging as valuable methods for diagnosing and treating tumor patients [16]. Given this growing body of evidence, it is clear that a deeper understanding of the gut-brain axis is crucial for developing effective strategies for the prevention and treatment of brain cancer. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed a strong connection between the disturbance of the gut microflora and the dysbiosis of key physiological processes, such as metabolism, cellular processes, and environmental information processing, in brain tumor patients [12]. Gut microbiota in brain tumor patients had a reduced role in the synthesis and decomposition of carbohydrates and the dysregulation of energy metabolism has been linked to the development of tumors [17]. Thus, the results suggest potential alterations in the metabolism and immune system of brain tumor patients.

Recent literatures suggest a potential association between the gut microbiome and brain tumors. Yuqi Wen et al. demonstrated that the oral microbiome may serve as a biomarker in differentiating glioma patients from healthy individuals [18]. Another study by Patrizz et al, found that

the gut microbiome can regulate the immune environment of gliomas via the gut-brain axis [19,20]. The gut microbial composition appears to be closely linked to the malignancy of brain tumors. Li, et al. unveiled substantial alterations in the gut microbiota composition associated with brain tumors [17]. For instance, at the phylum level, their findings demonstrated that the malignant brain tumor patients had the lowest abundance of Firmicutes [17]. Meanwhile, numerous studies have indicated that Firmicutes can control anti-inflammatory processes and apoptosis through the production of butyrate [12,21]. Meanwhile, in the malignant brain tumor group, heightened presence of Fusobacteria and Proteobacteria was observed [12]. Fusobacteria, being opportunistic pathogens, have been documented to boost tumor cell proliferation by regulating T regulatory cells and activating autophagy [22]. The abundance of *Fusobacterium mortiferum* was found to significantly increase in patients with intestinal adenomatous polyps [23]. Whereas, the abnormal increase in Proteobacteria abundance suggests a breakdown in the intestinal epithelial barrier, leading to increased vulnerability to infection [24]. In benign brain tumor, it has been depicted the lowest abundance of Actinobacteria, compared to the healthy group. Whereas, Actinobacteria, which are related to valeric acid, have been found to be diminished in colorectal tumors [25]. In addition, in benign mass Bacteroidetes was particularly enriched. Bacteroidetes has been reported to play an important role in the host through metabolic conversion. An imbalanced Bacteroidetes abundance could induce neuroinflammation through the excessive production of propionate [26], which has a dose-dependent impact on brain cell neurotoxicity and microglial activation [27]. Furthermore, the excessive presence of Bacteroidetes bacteria in brain tumors reduced the Firmicutes to Bacteroidetes (F/B) ratio which is associated with systemic inflammation and immunity dysbiosis [17]. Interestingly, correlation was observed between low F/B and a reduction in the levels of circulating short-chain fatty acids, which in turn can lead to metabolic dysfunction [17]. In specific brain tumor and pituitary adenoma (PA), Hu et al were divided patients showed that the microbial communities could be clearly differentiated between PA and healthy patients which specific species such as lower Oscillibacter sp. 57_20 and higher Clostridium innocuum played a significant role in pituitary adenoma patients. Furthermore, there was an increased ratio of Firmicutes to Bacteroidetes in both invasive pituitary adenoma (IPA) and non-invasive pituitary adenoma (NIPA) groups, compared to the healthy group. These species may serve as key indicators for identifying individuals at a higher risk for PA [28]. Previous studies have shown that *Clostridium innocuum* can cause inflammation, swelling, and tissue death, and it is a common cause of infections in some populations [29]. On the other hand, a lower Firmicutes/Bacteroidetes ratio was found to be associated with a decrease in body mass index (BMI), and a significant decrease in the abundance of the genus Oscillibacter was observed in patients with newly diagnosed acromegaly [30,31]. Moreover, the meningioma patients demonstrated increased in pathogenic bacteria such as Enterobacteriaceae, while the glioma group was characterized by over-representation of carcinogenic bacteria like Fusobacterium and Akkermansia [31]. This led to the creation of a microbial biomarker panel consisting of Fusobacterium, Akkermansia, Escherichia/Shigella, Lachnospira, Agathobacter, and Bifidobacterium, which was confirmed to have the ability to differentiate between brain tumor patients and healthy individuals [12].

The gut microbiome can play a significant role in systemic inflammation by producing pro-inflammatory compounds and altering the immune system. This can have a significant impact on brain health, as chronic inflammation has been implicated in the development and progression of several brain disorders, including brain cancer, Alzheimer's disease, and Parkinson's disease [32]. In addition to its role in neurotransmitter synthesis, the gut microbiome also modulates the immune system. The gut microbiome acts as a barrier against harmful pathogens and influences the production of immune cells, including T cells and B cells, which play a crucial role in defending against infections and diseases [33]. Fusobacteria, which are known for being opportunistic pathogens and elevate in malignant tumor, have been linked to promoting tumor cell growth by controlling T regulatory cells and activating autophagy [34]. Moreover, A study showed that Sutterella could greatly diminish the diversity of the microbial community by destroying IgA and advancing tumor progression [35]. Nie D, at al. [36] revealed disparities in both the composition and abundance of gut microbiota among growth hormone-secreting pituitary adenoma (GHPA) patients, nonfunctional pituitary adenoma (NFPA) patients, and healthy individuals [36]. Subsequent to undergoing Fecal microbiota transplantation (FMT), the gut flora in GHPA patients was found to enhance tumor development in mice models. This was evidenced by a rise in the quantity of programmed cell death ligand 1 (PD-L1) positive cells in tumor tissue and an increase in the infiltration of CD8+ cells. Furthermore, they detected elevated numbers of CD3+ CD8+ cells and heightened levels of soluble PD-L1 in peripheral blood. These results suggest that the gut microbiota of GHPA patients can stimulate tumor growth and that the immune system may play a role in this process [36]. In addition, the genera Bifidobacterium and Parasutterella are the cornerstone components of the gut microbiota, and the loss of these genera could lead to an imbalance in immunity, neurohormone, and metabolic systems [37]. The genera Escherichia/Shigella and Fusobacterium were also identified as biomarkers for malignant brain tumors [17]. In the benign brain tumor group, the genus Roseburia, which has potential as a probiotic for treating diseases, was significantly elevated

[17]. Its ability to regulate the brain's functional connectivity pattern through tumor necrosis factor-alpha (TNF-α) might explain this observation [38]. Additionally, several probiotic bacteria were identified as biomarkers for the healthy group. Jiang et al highlighted on experiment research that brain tumor patients, particularly those in the malignant glioma group, displayed significant dysbiosis in both the structure and function of their gut microbiota. In addition, a microbial panel consisting of Fusobacterium, Akkermansia, Escherichia/Shigella, Lachnospira, Agathobacter, and Bifidobacterium showed potential as biomarkers for brain tumor patients [12].

The gut microbiome can produce compounds that affect various aspects of tumor biology, including angiogenesis, tumor cell proliferation, and metastasis [39]. Angiogenesis, the formation of new blood vessels, is crucial for the growth and spread of brain tumors, and the gut microbiome has been shown to modulate angiogenesis through the production of various compounds [40]. Similarly, the gut microbiome can influence tumor cell proliferation and metastasis, the spread of cancer cells to other parts of the body, through its impact on the local microenvironment and the immune system [41].

Despite these findings, most related studies have limited sample sizes; one promising avenue for exploring the potential of the gut microbiome in the treatment of brain cancer is through the use of microbiome-based therapies. These therapies aim to modulate the gut microbiome and target the gut-brain axis in order to promote health and prevent disease. In the context of brain cancer, microbiome-based therapies may have the potential to target the gut-brain axis and modulate the gut microbiome in order to reduce systemic inflammation, prevent angiogenesis, and limit tumor cell proliferation and metastasis [42]. While much more research is needed to fully understand the impact of the gut microbiome on brain health and disease, the potential for microbiome-based therapies to promote health and prevent disease is extremely promising. A deeper understanding of the gut-brain axis and the role of the gut microbiome in the development and progression of brain cancer will be crucial for the development of effective therapies for the prevention and treatment of this debilitating disease (Appendix 1).

Conclusion

In conclusion, the potential role of the gut microbiome in the development and progression of brain tumors is a rapidly growing area of research. Our findings highlight the imbalanced gut microbial ecosystem associated with the severity of malignancy in brain tumor patients. The gut-brain axis has a significant impact on brain health and disease, and a deeper understanding of the interplay between the gut microbiome and brain cancer will be crucial for the development of new therapeutic strategies for the prevention and treatment of brain tumors. Further research is needed to fully understand the mechanisms by which the gut microbiome influences brain cancer and to develop microbiome-based therapies for the treatment of this devastating disease.

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