SCOPING REVIEW

Gut-Brain Axis, Notch, and Brain Cancer: 'The Rising Three'

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ABSTRACT

Background: The gut-brain axis (GBA) facilitates reciprocal communication between the central and enteric nervous systems. The connection between the GBA, Notch, and brain cancer is a complex and intricate subject that warrants further exploration. Brain cancer has a multifaceted pathophysiology and structure, making the journey from diagnosis to treatment challenging. The involvement of Notch in the signaling pathway could be relevant to both brain cancer and the gut-brain axis. **Objective:** This research aimed to examine the complex interplay between the gut-brain axis (GBA), Notch signaling, and brain cancer, specifically gliomas. **Material and Method:** This study was a scoping review conducted using multiple search engines, including PubMed, ProQuest, and Cambridge Core, spanning from 2018 to 2023. The collected materials were filtered and subsequently analyzed. **Result:** The existence of the gut-brain axis is a fascinating topic for in-depth exploration. The complex relationship between Notch and the gut-brain axis may offer valuable insights into the pathogenesis of brain cancer. The literature review identified two publications, which were analyzed in more detail. The gut-brain axis (GBA) refers to a bidirectional communication network between the central nervous system and the enteric nervous system, regulating gastrointestinal functions. The identification of the Notch signaling pathway suggests its role in the development of brain tumors. **Conclusion:** The connections between the gut-brain axis, Notch, and brain cancer are evident. The Notch pathway, as a signaling mechanism, is linked to brain cancer, and the gut-brain axis is also associated with it. This interconnected relationship has the potential to uncover novel avenues for diagnosis and therapy, warranting further research.

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Highlights

1. The gut-brain axis (GBA) is a bidirectional communication network linking the gastrointestinal tract and the central nervous system (CNS), involving neurons and various signaling molecules such as endocrine, humoral, metabolic, and immunological factors.
2. The Notch signaling pathway is implicated in the development of brain tumors, including

gliomas, which show elevated Notch receptor levels. This pathway is critical in tumor cell proliferation, survival, and invasiveness.

BACKGROUND

The gut-brain axis (GBA) establishes a connection between the gastrointestinal tract and the central nervous system, encompassing both physical and physiological aspects. The GBA is recognized as a bidirectional communication network that involves neurons and various signaling molecules, including endocrine, humoral, metabolic, and immunological factors, which traverse between the gut and the brain. This definition offers a holistic perspective of the human body, conceptualizing it as a host engaged in an ecosystemic, symbiotic relationship with the gut microbiome. This relationship is crucial in several areas, including immunity, nutrition, and overall well-being (Reynoso-García, et al., 2022). The impact of the gut microbiome on brain development has been strongly supported, particularly through preclinical investigations. Research on germ-free mice has provided substantial evidence regarding the developmental evolution of the enteric nervous system (ENS) under the influence of microbial colonization (Needham, et al., 2020). Furthermore, it has been discovered that the gut microbiota influences aging. However, it is important to note that the brain and the stomach are separate entities, partitioned by intrinsic barriers: the gut and blood-brain barriers (BBB).

The Notch receptors play a critical role in regulating essential cellular processes during both embryonic and postnatal development. The mammalian genome contains four paralogs of the Notch gene: Notch 1–4. These paralogs are activated by three ligands known as Delta-like (Dll1/3/4) and two ligands called Serrate-like (Jagged1/2). Additionally, scientists have identified noncanonical Notch ligands, such as epidermal growth factor-like protein 7 (EGFL7), which functions primarily to inhibit Notch signaling. The Notch signaling pathway is crucial for maintaining neural stem cells and directing neural progenitor cells toward the glial lineage by preventing neuronal differentiation in both the brain and the spinal cord. The association between Notch and the etiology of brain tumors is often observed due to the shared characteristics between tumor cells and neural stem and progenitor cells. Gliomas, for example, have been found to exhibit elevated levels of Notch receptors (Mehrian-Shai, et al., 2019). Their ability to promote cancer has been demonstrated through laboratory studies in controlled environments (in vitro) and living organisms (in vivo), where Notch receptor levels were altered to observe the effects (Mehrian-Shai, et al., 2019). The gut-brain axis consists of a complex network of blood and lymphatic vessels, enabling the microbiota to influence the brain. The gut microbiota has been identified as a potentially influential non-genetic factor in the development of brain tumors and the effectiveness of treatment approaches. The microbiota plays a key role in promoting cellular proliferation, suppressing apoptosis, and enhancing angiogenesis and invasiveness by modulating immune responses and inducing inflammatory processes. Additionally, altered microbial metabolites and their corresponding levels have the potential to stimulate cellular proliferation (Mehrian-Shai, et al., 2019).

In addition to playing a role in how tumors grow and spread, the gut-brain axis also has clear effects through the release of metabolites. Metabolites and other physiologically active substances produced in the gut and transported through the bloodstream can affect the immune system as a whole (Sharon, et al., 2014). Although there may be differences in microbial products among individuals in good health, the metabolic activity of the gut microbiome appears to be fairly consistent. Nevertheless, significant alterations in this balance can arise as a result of disruptions to the microbiome. The application of mass spectrometric techniques revealed discernible variations in metabolites present in plasma extracts obtained from germ-free mice compared to those derived from conventional animals. Furthermore, it was observed that the presence of gut bacteria directly influences the host's drug-metabolic capabilities (Mehrian-Shai, et al., 2019). In addition to neurotransmitters and neuromodulators associated with the central nervous system (CNS), the gut microbiota also generates metabolites, specifically short-chain fatty acids (SCFAs). Proinflammatory cytokines are released less often in the presence of these SCFAs. Instead, SCFAs promote the production of interleukin-10 (IL-10) and the formation of regulatory T cells (Tregs). A portion of the circulating short-chain fatty acids (SCFAs) may also traverse the CNS. Furthermore, the integrity of the blood-brain barrier (BBB) is compromised during neuroinflammation

due to the influence of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Almutairi, et al., 2016).

The interplay among these three factors plays a significant role, particularly in the pathophysiology of brain cancer. Activation of the Notch signaling system has been observed to stimulate the development of brain tumors. This assertion is substantiated by the involvement of the gut-brain axis, wherein an imbalance in the microbiome can lead to upregulation of the Notch signaling system, thus promoting the development of malignancies. This study provides a comprehensive analysis of the topic, exploring the subject matter with clarity and precision.

OBJECTIVE

This study was to explore the intricate relationship between the gut-brain axis (GBA), Notch signaling, and brain cancer, particularly gliomas.

MATERIAL AND METHOD

The approach chosen for this study was a scoping review, specifically an evidence-based literature review. This approach involves examining relevant literature sources on the relationship between the gut-brain axis, Notch signaling, and brain cancer. The literature search focused on data published between 2018 and 2023. Data collection was carried out using secondary data obtained through various search engines, such as PubMed, ProQuest, and Cambridge Core. The collected data were then analyzed and subjected to data reduction techniques. The study incorporated three key terms as keywords: "gut-brain axis," "Notch," and "brain cancer." Inclusion criteria were limited to articles written in English and available in full. The exclusion criteria encompassed articles that were not fully accessible and comprehensive literature review studies. After processing, the materials were presented and categorized according to their journal of origin. The steps involved in the data search, including the PRISMA flowchart, are shown in Figure 1.

RESULT

A table showing a summary of the journals that were analyzed can be seen in Table 1.

Table 1. Summary of the journal analysis.

Journals	Keynotes
Zhang, et al., 2022 doi: 10.3389/fcimb.2022.1072341.	Investigating the specific mechanisms by which external factors, such as stress, physical exercise, diet, and medications, influence neurogenesis via the microbiota-gut-brain axis. This research explored the direct effects of these external factors on the composition of the gut microbiota and their subsequent impact on neurogenesis. Understanding how these factors modulate microbiota diversity and activity may provide insights into their role in brain health and neuroplasticity. Exploring the potential of traditional Chinese medicine (TCM) compounds in modulating the gut microbiota to influence adult neurogenesis. Investigating the mechanisms by which TCM compounds regulate gut microbiota composition and their subsequent effects on neurogenesis could uncover novel therapeutic approaches for treating neurological diseases. This could involve identifying specific bioactive compounds in TCM and their interactions with microbiota and neuronal pathways.

	Investigating the role of specific bacterial phyla and their metabolites in modulating neurogenesis through the microbiota-gut-brain axis. The research focused on understanding how specific gut microbiota components, including bacterial phyla and their metabolites, influence neuronal development and immune responses. These studies could provide valuable insights into the complex interactions within the microbiota-gut-brain axis and their contribution to neurogenesis, ultimately informing potential therapeutic strategies for neurodegenerative conditions.
Dono, et al., 2022 doi: 10.1093/noajnl/vdac054.	Investigating the relationship between gut microbiome composition and fecal metabolites in glioma patients to identify potential biomarkers that could be associated with survival outcomes. This study aimed to explore how variations in the gut microbiome and its metabolites correlate with clinical outcomes, with a focus on identifying biomarkers that may serve as predictors of survival in glioma patients. Evaluating the potential use of probiotics or fecal transplants to modulate the gut microbiome and enhance therapeutic strategies for gliomas, particularly in the context of immunotherapy and viral therapy. This research assessed how interventions such as probiotics or fecal microbiota transplantation may influence the gut microbiome and improve therapeutic responses in glioma patients, with an emphasis on the synergy between microbiome modulation and immunotherapies or viral treatments. Exploring the presence and impact of intratumoral bacteria in gliomas, including investigations into potential causality, leakage from ruptured vasculature, and the relationship between bacterial presence and the immunosuppressive tumor microenvironment. This study focused on understanding the role of intratumoral bacteria in gliomas, investigating whether they contribute to tumor progression, how they may enter through compromised blood vessels, and how they interact with the tumor's immune evasion mechanisms.

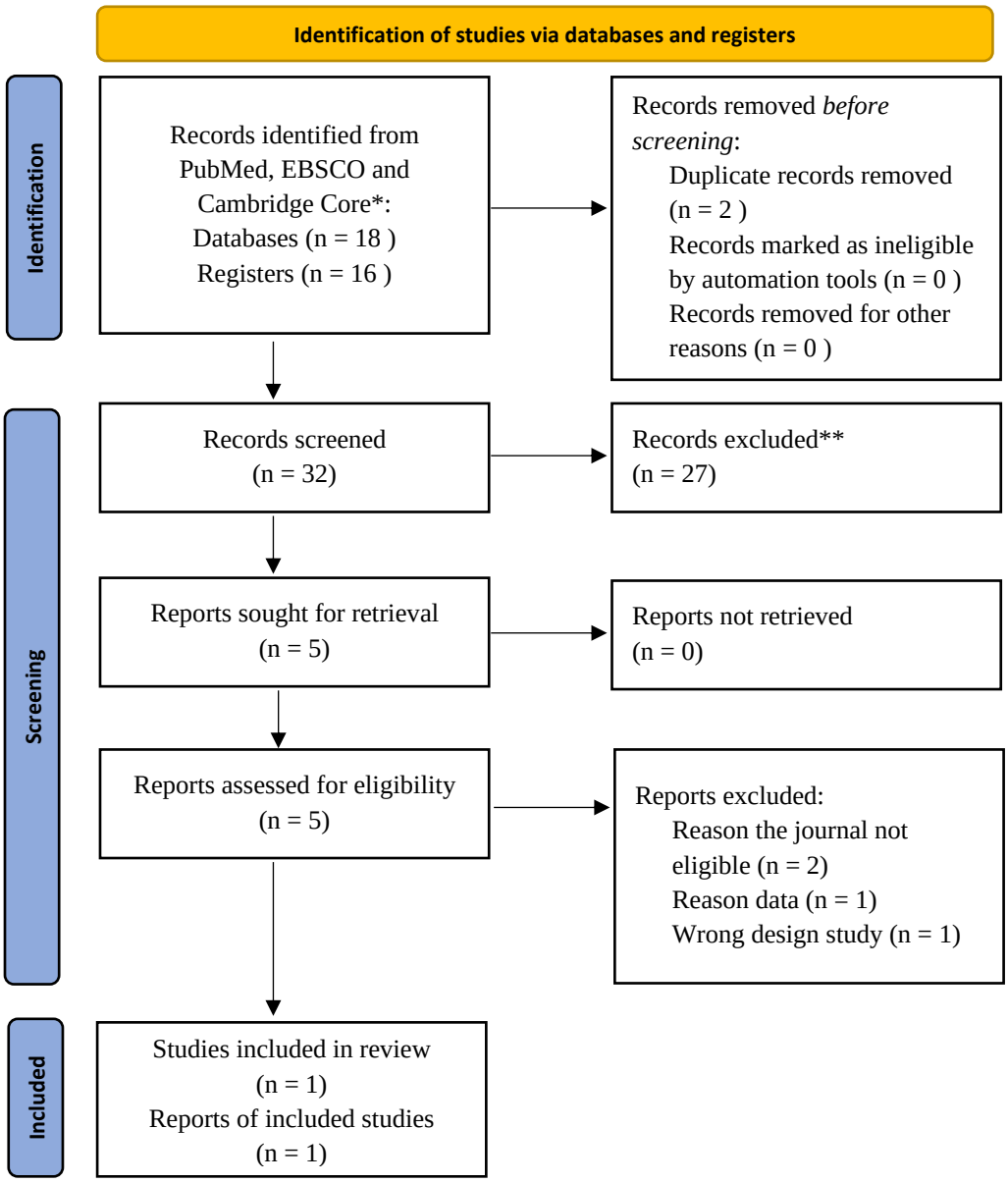

Figure 1. ScR PRISMA flowchart for studies of gut brain axis, Notch and brain cancer.

DISCUSSION

Microbiota in gut brain axis

The available evidence from both clinical and experimental settings indicates that the gut-brain axis (GBA) is significantly influenced by the intestinal microbiota. These microorganisms interact not only with intestinal cells and the enteric nervous system (ENS) but also have direct connections with the central nervous system (CNS) through metabolic and neuroendocrine pathways. A study conducted over twenty years ago provided compelling evidence that established a correlation between gut microbiota and the human brain. This information was derived from a group of individuals diagnosed with hepatic encephalopathy, who reported significant improvements after receiving oral antibiotic treatment. This observation suggested that the treatment led to improvements in their condition. More recent research continues to highlight the important role of gut bacteria in influencing anxiety- and depression-like behaviors (Foster & McVey Neufeld, 2013; Naseribafrouei, et al., 2014). Additionally, dysbiosis has been shown to significantly impact the onset and expression of autism spectrum disorder. It has been observed that individuals with autism spectrum disorder exhibit notable alterations in their microbiome composition, which correlate with the severity of their condition (Mayer, et al., 2014).

Dysbiosis can also manifest in functional gastrointestinal disorders (FGIDs), which are strongly associated with mood disorders and are accompanied by changes in the gut microbiota's composition (Berrill, et al., 2013; Simrén, et al., 2013). Empirical evidence suggests dysfunctions in the bidirectional communication between the brain and the gastrointestinal system, particularly in relation to irritable bowel syndrome (IBS). Dysfunction in the gastrointestinal barrier can lead to changes in visceral hypersensitivity, alterations in the motility and secretion of substances in the gastrointestinal tract, and cellular disruptions in the immune and enteroendocrine systems. Research indicates that the microbiota can interact with various pathophysiological targets connected to IBS, as supported by multiple lines of evidence (DuPont, 2014). Key findings include changes in the microbiota composition of individuals with IBS, characterized by instability and reduced diversity. Additionally, there is an association between post-infectious IBS and the presence of small intestinal bacterial overgrowth. Furthermore, certain probiotics and non-systemic antibiotics have been shown to effectively treat IBS (Quigley, 2014). Earlier studies also demonstrated that the visceral hypersensitivity phenotype, a prominent feature of IBS, can be transferred from IBS patients to germ-free rats by transplanting microbiota from IBS patients (Crouzet, et al., 2013). This phenomenon highlights the role of the gut microbiota in the development of visceral hypersensitivity in IBS. Moreover, the simultaneous dysregulation of the GBA (glucocerebrosidase) enzyme and the gut microbiota in the pathophysiology of IBS has led to the hypothesis that IBS should be understood primarily as a condition involving the interaction between the microbiota and the GBA enzyme, rather than being exclusively attributed to microbiome-related factors (Kennedy, 2014).

Brain cancer and gut-brain axis

Cancers affecting the central nervous system (CNS) are among the leading causes of death in both adults and children diagnosed with these diseases. Research into the molecular etiology of these debilitating disorders has revealed numerous genetic abnormalities that impact cell survival and DNA repair pathways. However, therapies tailored to these pathways have often proven ineffective or have shown only modest improvements in survival. Brain neoplasia triggers a process of immune suppression, creating a tumor microenvironment that facilitates tumor growth (Nduom, et al., 2015; Siegel, et al., 2016; Silver, et al., 2016). This presents an additional challenge in developing a universal, effective treatment for all types of tumors. Understanding how immune suppression is initiated is a crucial step in limiting carcinogenesis. Current efforts in immunotherapy aim to disrupt these immune-suppressive pathways and stimulate the immune system to target growing tumors (Bush & Butowski, 2017; Mangani, et al., 2017; Touat, et al., 2017; Noch, et al, 2018). The brain is considered an immune-privileged organ due to a mechanism known as the blood-brain barrier (BBB), which restricts immune cell entry. Microglial cells, which are the brain's resident immune cells, play a key role in modulating its natural immunological functions. Microglia can be polarized into two distinct states: the M1 state, which promotes tissue destruction, and the M2 state, which promotes tissue regeneration. T helper cells (Th cells) are cytokine-producing T lymphocytes involved in immune responses. Th1 cells produce proinflammatory cytokines that promote inflammation, while Th2 cells produce anti-inflammatory cytokines such as interleukin-10 (IL-10) (Watt, et al., 2017). In response to pathogens, microglia activate T cells and release proinflammatory cytokines such as TNF, IL-6, and IL-1. Subsequently, Th2 cells produce cytokines like IL-4 and IL-13, which downregulate the inflammatory response and cause microglia to transition from the M1 to the M2 state. The uncontrolled remodeling of tissue, driven by microglial activation, can contribute to the development of brain tumors (Carabotti, et al., 2015). High-grade gliomas often exhibit elevated levels of CSF1, a cytokine produced by microglia and macrophages, and its receptor CSF1R, which mediates its effects (De, et al., 2016). In glioblastomas, Th2 cytokines such as IL-6 and TGF are expressed at high levels, while Th1 cytokines like IL-2 and IL-12 are notably absent. The maturation of microglia is impaired in the absence of a microbiome, which severely limits their response to infectious agents. However, the introduction of a microbiome has been shown to alleviate the symptoms of certain types of microglial dysfunction (Sharon, et al., 2014; Erny, et al., 2015).

When gliomagenesis occurs, the blood-brain barrier (BBB) is compromised, allowing circulating immune cells to infiltrate the tumor microenvironment (Gieryng, et al., 2017). These cells include T cells, B cells, macrophages, and myeloid-derived suppressor cells. The bidirectional interaction between immune cells and glioma cells creates an immunosuppressive milieu that supports tumor

survival and progression. Microglia and macrophages, which are recruited to thmgg7e glioma site, can polarize into M2 macrophages, which promote tumor growth and further suppress immune function (Galvão & Zong, 2013; Wu, 2017). Elevated levels of M2 macrophages are associated with glioblastoma multiforme (GBM) and correlate negatively with patient survival. Activated microglia secrete cytokines and growth factors such as IL-10, EGF, and VEGF, all of which stimulate tumor cell proliferation and angiogenesis. Moreover, IL-10 inhibits T cell proliferation and maintains an immunosuppressive state. Several studies by Prosniak, et al., (2013), Hambardzumyan, et al., (2016), and Lisi, et al., (2017) have shown that these cells fail to induce a cytotoxic state in CD8+ T cells, as they cannot release proinflammatory cytokines such as IL-6, IL-1, and TNF.

Gliomas are further characterized by an immunosuppressive microenvironment, in part due to increased numbers of regulatory T cells (Tregs), which produce high levels of IL-10 and TGF. Tregs are considered the principal regulators of immunosuppression in the glioma microenvironment (Ooi, et al., 2014). The number of Tregs has been found to correlate with the World Health Organization (WHO) grade of the tumor. In mouse models of glioma, reducing Treg numbers has been shown to improve survival outcomes (Mehrian-Shai, et al., 2019). Natural killer (NK) cells, part of the innate immune system, possess the ability to eliminate tumor cells without prior sensitization. Factors such as IL-2 and IFN-γ enhance the immune response by promoting the activation and expansion of T and NK cells, thus boosting the immune system's capacity to detect and destroy cancer cells (Rini, 2014). Conversely, the downregulation of NK cell function in brain tumors may be partly attributed to elevated plasma levels of TGF (Poli, et al., 2013). Interestingly, glioma prevalence is lower in individuals with allergies and autoimmune diseases, conditions that involve ongoing immune activation. This observation underscores the importance of maintaining a balanced immune function while also reducing Treg activity to combat brain tumor development. Therefore, appropriate modulation of both the microbiota and microglia could be crucial for the prevention and treatment of brain tumors, as immune suppression is diminished when these cells work in concert (Mehrian-Shai, et al., 2019).

Notch and gut-brain axis

Metabolites and other physiologically active compounds produced in the gut can circulate or be actively transferred into the bloodstream, thereby influencing the immune response systemically. While the metabolic activity of the gut microbiome remains relatively stable despite variations in its composition among healthy individuals, any disruption to the microbiome can lead to significant shifts in this equilibrium (Mehrian-Shai, et al., 2019). Short-chain fatty acids (SCFAs), as well as CNS-related neurotransmitters and neuromodulators, are produced by the gut microbiota (Sun, et al., 2022). These metabolites suppress the production of proinflammatory cytokines, promote the formation of regulatory T cells (Tregs), and stimulate the secretion of IL-10. Some of the circulating SCFAs may also enter the central nervous system (CNS) (Sarkar, et al., 2016). Moreover, inflammatory cytokines such as IL-1, IL-6, and TNF compromise the integrity of the blood-brain barrier (BBB), contributing to neuroinflammation. It remains unclear whether the mediators or metabolites produced by the microbiota directly impact the BBB and contribute to immune suppression within the CNS (Sarkar, et al., 2016).

A growing body of research suggests that the gut microbiota influences brain function and behavior through neuronal, endocrine, and immune mechanisms. The gut bacteria play a role in the maturation of the central nervous system, highlighting the importance of ongoing investigations into the lymphatic arteries of the brain. These studies suggest a potential link between brain cancer, the immune system, and inflammation (Dissing-Olesen, et al., 2015; Raper, et al., 2016). Recent findings have provided empirical evidence supporting the connection between the lymphatic network and the CNS, particularly regarding lymph nodes involved in CNS drainage. Disruptions to this network may significantly influence the development of brain cancer. It is hypothesized that the microbiome may contribute to the initiation or progression of brain tumors by modulating immune cells or metabolites that reach areas of the body prone to cancer (Mayer, et al., 2014).

Brain cancer and Notch

Gliomas account for approximately 30% of all brain tumor cases and over 80% of malignant brain tumors (Ostrom, et al., 2014). Gliomas are generally categorized into two main types: diffuse low-grade and intermediate-grade II-III gliomas, also known as low-grade gliomas (LGGs), and grade IV gliomas, which are more aggressive and referred to as glioblastoma multiforme (GBM). Low-grade gliomas

(LGGs) are challenging to remove surgically due to their fragmented and invasive nature (The Cancer Genome Atlas Research Network, 2015), often leading to tumor recurrence and progression into higher-grade gliomas. While individuals with LGGs often have a more favorable prognosis, complete neurosurgical resection remains difficult because of the tumors' inherent characteristics. It is noteworthy that approximately 20% of glioblastomas (GBMs) are secondary tumors, originating from pre-existing low-grade gliomas (LGGs) (Bai, et al., 2016). Advances in omics technologies have recently facilitated the integration of clinical and histological data with comprehensive analyses of gliomas' genetic, epigenetic, expression, and metabolic profiles (Reifenberger *et al.*, 2017). This approach has revealed a heterogeneous landscape of glioma subtypes, each with distinct survival rates and responses to therapy. Consequently, the World Health Organization (WHO) has included molecular criteria in the diagnostic protocol for gliomas, in addition to conventional histological markers. The controversial role of Notch signaling in gliomas can be attributed to the considerable heterogeneity within these tumors and the context-dependent nature of Notch signaling across different malignancies, even within the same tumor type (Louis, et al., 2016).

Notch signaling plays a critical role in maintaining the identity of neural stem cells (NSCs) and progenitors, as well as in controlling cell fate decisions in both developing and adult brains. Understanding the regulatory mechanisms behind these processes is essential for effectively targeting cancer-initiating cells. Gliomas can develop when NSCs and glial progenitors proliferate too rapidly and fail to differentiate properly (Alcantara Llaguno, et al., 2019). In the adult mammalian brain, NSCs persist in two regions: the subgranular zone of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles (Giachino & Taylor, 2014; Bond, et al., 2015). Most adult NSCs remain in a quiescent state, with only a small fraction actively proliferating at any given time. This process is vital for maintaining the self-renewal potential of NSCs and generating intermediate progenitor cells (IPs). In contrast, induced pluripotent (IP) cells exhibit robust proliferation and differentiation, primarily giving rise to neuroblasts, while adult neural stem cell niches retain the capacity to generate glial cells (Gage & Temple, 2013; Navarro Negredo, et al., 2020). This delicate balance is governed by multiple processes that ensure the production of neurons while maintaining a stem cell pool, providing a continual supply of NSCs for brain function.

Notch as an oncogene in glioma

The activation of Notch signaling has been shown to enhance the aggressiveness of gliomas under certain conditions. Glioma stem cells (GSCs) possess enhanced DNA repair capabilities and higher levels of ATP-binding cassette (ABC) multidrug transporters compared to other glioma cell types, contributing to increased resistance to treatment. GSCs can differentiate into less-tumorigenic cancer cells, which make up the majority of the tumor mass (Lathia, et al., 2015). Notch signaling, similar to its role in maintaining the normal characteristics of neural stem cells (NSCs), can also enhance stem cell properties within brain tumors, making it a promising target for therapeutic interventions.

Notch signaling is widely expressed in various glioma cell types, as confirmed by data from both human tumor samples and mouse glioma models (Giachino & Taylor, 2014). Studies have shown that blocking Notch1/2 or using gamma-secretase inhibitors (GSIs) is more effective in targeting CD133-positive GSCs compared to CD133-negative glioma cells. In vivo experiments with glioma xenograft models demonstrated that inhibiting Notch signaling or RBPJ reduces tumor growth and self-renewal (Xie, et al., 2016). However, increasing NICD levels has been shown to prolong cell survival by altering radioresistance and side population phenotype in glioma cells. Nevertheless, this overexpression alone is insufficient to induce tumor formation in the mouse brain (Natarajan, et al., 2013).

The combination of GSIs and radiation has proven to be more effective in suppressing tumor self-renewal than radiation alone. This synergistic effect is mainly due to Notch signaling activation, which enhances the phosphorylation of Akt and Stat3 (Parmigiani, et al., 2017). Furthermore, Notch signaling promotes a more aggressive glioma phenotype by downregulating the tumor suppressor protein PML and upregulating the oncogenic long non-coding RNA TUG1 (Katsushima, et al., 2016). Using RNA interference to target Notch ligands, such as Jagged1 or Dll1, reduces the survival and proliferation of glioma cells across different cell lines. Increased Jagged1 expression correlates with poor prognosis in glioma patients (Sarkar, et al., 2016). Tenascin-C and Jagged1, extracellular matrix glycoproteins, may enhance each other's production, creating a feedback loop that could promote tumorigenesis (Sarkar, et

al., 2016; Parmigiani, et al., 2017). However, excessive Jagged1 expression may disrupt normal Notch signaling in glioma cells, potentially through the intracellular domain of Jagged1 (Lim, et al., 2015).

Notch signaling is crucial for maintaining the pool of dormant NSCs in the subventricular zone (SVZ) of adult brains (Engler, et al., 2018). These cells exhibit resistance to antimitotic therapies and have the capacity to replenish more proliferative progenitor cells. In glioblastoma (GBM) mouse models, temozolomide has been shown to promote tumor growth by activating chemotherapy-resistant glioma cells that are in a quiescent state. Inhibition of receptor tyrosine kinases (RTKs) leads to the formation of slow-cycling, drug-tolerant cells in PDGFRA-amplified human glioma cell lines. Increased Notch signaling activity facilitates the transition to this persistent, drug-tolerant state (Liau, et al., 2017). However, resistance to RTK inhibition can develop independently of Notch signaling in certain cell clones (Eyler, et al., 2020). These findings suggest that Notch signaling increases cellular plasticity and promotes the development of drug resistance in gliomas, potentially by enhancing stem cell proliferation.

Blocking Notch signaling has been shown to encourage differentiation of glioblastoma stem cells (GSCs) into terminal neurons by increasing the proneural transcription factor ASCL1 (Park, et al., 2017; Rajakulendran, et al., 2019). Adult NSCs in the SVZ reside in a specialized vascular microenvironment that maintains their stem cell-like properties and prevents differentiation. Endothelial cells within this niche release factors that promote Notch-dependent transcription, crucial for stem cell maintenance (Ottone, et al., 2014). Similarly, GSCs in gliomas are thought to reside near blood vessels, influenced by signals from endothelial cells in a manner similar to the SVZ niche. Nitric oxide, for example, has been shown to support stem-like features in PDGF-driven gliomas by activating Notch signaling (Parmigiani, et al., 2017).

Hypoxia, a common feature of gliomas, increases vasorin expression, which stabilizes NICD and enhances Notch signaling, especially in tumor regions with low oxygen levels. This has been linked to increased tumor aggressiveness. Additionally, dormant populations of GSCs have been found near the leading edge of tumors, where nerve fibers produce Jagged1, activating Notch1 and CD133, which contributes to tumor invasion through white matter tracts. This process is regulated by the SOX9, SOX2, and Notch1 signaling cycle (Man, et al., 2018; Rusu, et al., 2019; Wang, et al., 2019).

The significance linked between those threes

The endeavor to establish a direct association between the gut-brain axis, Notch signaling, and brain cancer presents significant obstacles. No definitive association could be found, as the papers discussing these three topics only provided insights into their prospective occurrences. However, through a thorough analysis of two academic publications, it was discovered that there are recurring motifs that can be seen as a cohesive element in understanding the interconnectedness of these three entities. The Notch pathway is thought to play a significant role in regulating neural stem cells (NSCs) during brain development in both embryos and adults (Zhang, et al., 2022). This pathway plays a crucial role in regulating the population of NSCs during various phases of development, ensuring balanced and optimal growth and maturation of the central nervous system. This information is supported by studies conducted by Androutsellis-Theotokis, et al., (2006), Mizutani, et al., (2007), and Imayoshi, et al., (2013). The regulation of this process is governed by transcription factors, namely the Wnt and Notch signaling pathways, as well as the extracellular matrix and a wide range of growth factors. Various external factors, such as stress, physical activity, nutritional intake, and pharmaceutical agents, may also have an impact. Presently, there is a wealth of data supporting the significant influence exerted by gut bacteria on the regulation of neuronal and glial function. The phenomenon under investigation is attributed to the microbiota-gut-brain (MGB) axis, which consists of the enteric nervous system, central nervous system (CNS), and the immune system (Cryan, et al., 2019; Gershon & Margolis, 2021).

The gut microbiota engages in bidirectional communication with the brain through the actions of its metabolites, which can traverse the blood-brain barrier (BBB), interact with the vagus nerve, or elicit immunological reactions in peripheral areas (Morais, et al., 2021). It was found that Notch1, RBP-J, Hes1, and Hes2 were more highly expressed in the dentate gyrus (DG) and the olfactory bulb (Sun, et al., 2022). The research suggests that the application of traditional Chinese medicine may impact the composition of gut flora. Therefore, it is possible that the Notch pathway could be affected, which may lead to changes in the differentiation of neural stem cells (NSCs). Thus, alterations in the types of microbiota in the gut can influence the growth of NSCs and the process of neurogenesis. The presence

and composition of gut microbiota can modulate the expression of Notch ligands and receptors, as well as the function of NSCs and the neurogenesis process to some extent (Zhang, et al., 2022).

Furthermore, the axis between the gut microbiota and the human body has the potential to significantly impact the etiology of several diseases, including brain cancer. The manipulation of the gastrointestinal microbiota is an emerging and insufficiently explored area of research that shows promise for enhancing the effectiveness of glioma treatment (Dono, et al., 2022). Recent studies in the field of neuro-oncology have revealed that gliomas influence the bacterial composition of the gut microbiome, fecal metabolites, and the innate immune system (D'Alessandro, et al., 2020; Patrizz, et al., 2020; Dono, et al., 2022).

Strength and limitations

The strength of the paper lies in its clear explanation of the correlation between brain cancer, Notch signaling, and the gut-brain axis. It provides a comprehensive understanding of how these three factors are interconnected, potentially enhancing the diagnosis and early treatment of brain cancer. However, further research is needed to address the limited number of studies and publications, particularly in the field of clinical research, to provide concrete evidence for the relationship between Notch signaling and the gut-brain axis in the diagnosis and treatment of brain cancer.

CONCLUSION

This article provides an in-depth examination of three emerging research areas: the complex relationship between the gut and the brain, the crucial role of the Notch pathway, and the intricate connection between brain cancer and its various aspects. These topics are both innovative and captivating, highlighting the need for further research. The importance of this research is evident, emphasizing the necessity for continued investigation, particularly in the realm of clinical research. Additional studies are needed to explore the underlying mechanisms of this treatment strategy and assess its potential clinical relevance.

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Conflict of Interest

None.

Funding Disclosure

None.

Author Contribution

GSM and NA contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, statistical expertise, obtaining of funding, and collection and assembly of data.

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