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Topic

Gut Microbiota's Involvement in Brain Tumors

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YB. Ansar/K. Radia Imene

Dedication

This work is wholeheartedly dedicated to my beloved parents. I am incredibly fortunate to have parents who believe in me, even during the times when I lacked belief in myself; they saw my strengths, talents, and abilities when I couldn't see them. When I faced moments of doubt and uncertainty, it was their steadfast belief that pushed me forward.

To my sisters , relatives and friends who were there through the breakdowns and the failures, telling me I am better than I believed I am , listening to my complaints , easing my fears, and rationing me into impossible situations…

For everyone who was my pack ….

I dedicate this work.

Youcef Brahim Ansar

I dedicate this work to my parents, whose unwavering support and constant encouragement have been essential in my journey. I am truly grateful and deeply honored to have you as parents. My gratitude towards you is beyond what words can convey.

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Abbreviations

ABT group: Anti biotic treated group

ANS: Autonomic Nervous System

BAAT: Bile acid-CoA: amino acid N-acyltransferase

BACS: Bile acid-CoA Synthetase

BAs: Bile Acids

BBB: Blood Brain Barrier

BMSB: Bacterial Metabolite Sodium Butyrate

CCK: Acetylcholecystokinin

CNS: Central Nervous System

CTLA4: Cytotoxic T-lymphocyte-associated protein 4

CYPs: Cytochromes P450

EGFRvIII: Epidermal growth factor receptor variant III

ENS: Enteric Nervous System

FACS: Fluorescence-Activated Cell Sorting

FGF19: Fibroblast growth factor 19

FOXp3: Forkhead box protein3

FXR: Farnesoid X receptor

GBA: Gut brain axis

GBM: Glioblastoma

GF: Germ free

GI: Gastro Intestinal

GM: Gut microbiota

Abbreviations

GPCRs: G protein-coupled receptor

HDAC: Histone deacetylase

HPA: Hypothalamic Pituitary Axis

HuM: Humanized mouse lines

IDH: Isocitrate dehydrogenase

ISAPP: International Scientific Association for Probiotics and Prebiotics

Mtorc2: Mammalian target of rapamycin (mTOR) complex 2

NMRI: Naval Medical Research Institute

PAMPs: Pathogen-associated molecular patterns

PD-1: Programmed cell Death 1

PD-L1: Programmed Death Ligand 1

PGN: Peptidoglycan

PRRs: Pattern recognition receptors

P75NTR: Neurotrophin Receptor p75

rDNA: Recombinant deoxyribonucleic acid

RICTOR: Rapamycin-insensitive companion of mammalian target of rapamycin

SCFAs: Short-chain fatty acids

TIM3: T-cell immunoglobulin mucin 3

Tp53: Transformation-related protein 53

VN: Vagus Nerve

Introduction

The intricate relationship between the gut and Central Nervous System (CNS), commonly referred to as the "gut-brain axis", has captivated the attention of researchers for numerous years.

Within the human gut, abundant and diverse microbial communities coexist. The gut is a highly dynamic ecosystem where resides a vast array of microbiota constituents, including bacteria, archaea, fungi, and other species **(Ma *et al.*, 2019)**. It has recently become evident that the gut microbiota has the ability to impact physiological aspects of the body **(Mittal *et al.*, 2017)**. The host's metabolism, inflammation, and immune response can be influenced by variations in the gut microbiota known as "dysbiosis" **(Li *et al.*, 2022)**.

Growing evidence suggests that the composition and by products of the gut microbiota play a pivotal role in various cerebral disorders, facilitated by a bidirectional communication pathway. The gut–brain communication is made possible by vagal/nervous and blood/lymphatic routes among others and pave the way for reciprocal modulation of CNS functions **(D'Alessandro *et al.*, 2021)**. The gut microbiota produces and consumes a wide range of molecules, that reach their cellular targets through different pathways, such as short-chain fatty acids (SCFAs) and neurotransmitters, that have the ability to modulate the CNS microenvironment, influence immune responses, and disrupt the endocrine system **(Li *et al.*, 2022)**.

Differences in the relative abundance, the composition and function of the gut microbiome between healthy individuals and patients have been described for a range of human diseases including autoimmune, metabolic and neurodegenerative diseases as well as cancer **(Benakis *et al.*, 2020)**.

While the field is still evolving and further research is needed, the present review highlights and discusses the results obtained until now about the intriguing connection between the gut microbiota and CNS and its potential involvement in brain tumors.

Chapter I

Literature Review

1 The gut microbiota system

The human gut is colonized by more than 100 trillion microbes cells (~ 4 x 10'13) weighing around 1-2 kg and identified as "the gut microbiota". It progressively stabilizes after birth and develops into an adult form after 3 years. The collective genetic material of all the bacteria, viruses, fungi, archaea and eukaryotes, also known as the "second human genome" is called microbioma **(Ferranti *et al.*, 2014)**.

The gut microbiota composition is not identical in all human bodies, due to different dietary habits, lifestyle *etc* **(Rinninella *et al.*, 2019)**. A healthy gut microbiota is predominantly constituted of the different phyla described in **table I (Jandhyala, 2015)**.

Gut microbial species play an important role in the maintenance of normal human health, through maintaining immune homeostasis, synthesis of important vitamins such as vitamin K and vitamin B12 **(Rowland, 2018)** also by suppressing the growth and colonization of pathogens **(Kho *et al* ,2018)**.

The Microbiota can be modulated by many environmental factors and also the genetics of the host (**Figure 1**). An alteration in the amount and function of the intestinal microorganisms, known as gut microbiota dysbiosis can be the cause of cardiovascular, metabolic, neurological diseases (Alzheimer, Parkinson, autism...) and cancer **(Illiano *et al.*, 2020)**.

Table I: Composition of a healthy gut microbiota.

Phylum	*Type of bacteria*	*Most common genera*	*Role*	*References*
Firmicutes	Gram positive bacteria	*Bacillus,Clostridium, Enterococcus,Lactobacillus*	• Responsible of SCFAs synthesis which have a major role in metabolism.	**(Stojanov *et al*., 2020)**
Bacteroidetes	Gram negative bacteria	*Bacteroides Alistipes Parabacteroides Prevotella*	• Regulate the immune system through cytokine synthesis which is considered to be a result of the interaction between their components, flagellin and lipopolysaccharides, with cell receptors.	**(Stojanov *et al*., 2020)**
Actinobacteria	Gram positive bacteria	*Bifidobacteria*	• Widely used as probiotics and have shown interesting roles in many pathological conditions.	**(Ait Barka *et al*.,2015)** **(Binda *et al*., 2018)**

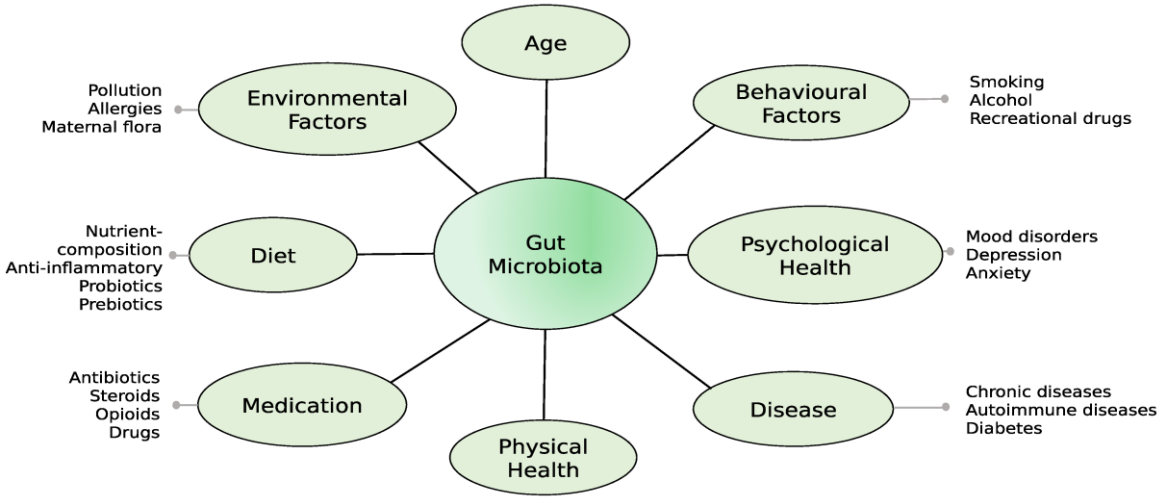

Figure 1: Factors influencing the microbiome. Microbiota can be modulated by physical health (such as practicing sport), Age (as getting old, microbial diversity decrease in the gut) **(Fart *et al.*, 2020)**.

2 Communication microbiota/brain:

2. 1 The gut -microbiota-brain axis: (GBA):

Also known as 'the gut-brain connection', was discovered by Ivan Pavlov, the first physiologist who was awarded the Nobel Prize in Physiology or Medicine in 1904.

GBA represents a network of connections involving multiple biological systems, allowing bidirectional communication between gut bacteria and the brain (CNS). It is essential for maintaining the homeostasis of the gastrointestinal, central nervous and microbial system.

Communication pathways in these biological networks include direct and indirect signals through chemical messengers, neural pathways, and the immune system **(Morais *et al.*, 2021)**.

As shown in **figure 2**, the GBA links emotional and cognitive centers of the brain with peripheral intestinal functions. The gut-brain communication network encompasses the central nervous system (CNS), the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axis. The ANS, including the sympathetic and parasympathetic limbs, drives both afferent signals, arising from the lumen and transmitted though enteric, spinal and vagal pathways to CNS, and efferent signals from CNS to the intestinal wall **(Carabotti *et al.*, 2015)**.

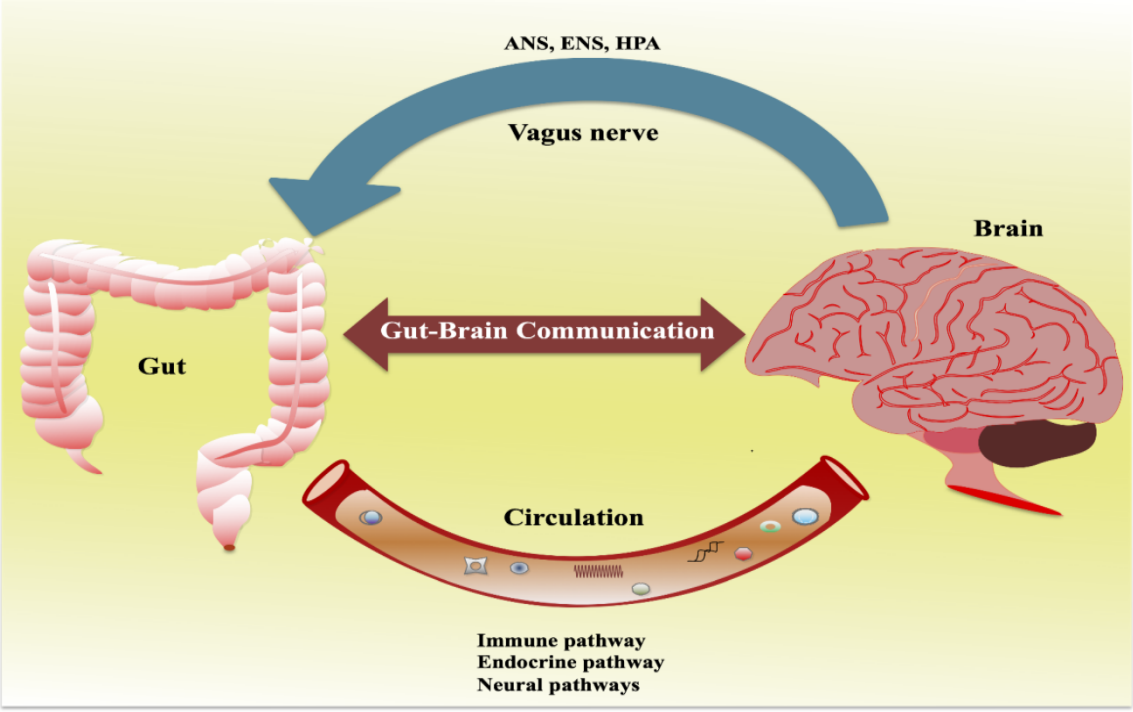

Figure 2: Communication pathways of the microbiota-gut-brain axis. The crosstalk of the microbiota-gut-brain axis mainly comprised of four modules: metabolic, neural, immune, and endocrine signaling pathways **(Lin *et al.*, 2020)**.

2. 2 Microbiota and GBA:

Research have shown that microbiota influences CNS functions such as anxiety and depressive behaviors. Patients with brain disorder present specific microbiome alterations depending on the severity of the disease **(Foster *et al.*, 2013)**.

The International Scientific Association for Probiotics and Prebiotics (ISAPP) reviewed and discussed the role of gut bacteria on epithelial cell function, gastrointestinal motility, visceral sensitivity, perception and behavior. The review was established through current available data, mostly gathered from animal studies (mice and rats) evaluating the effect of the gut microbiota and/or changes induced by probiotic and prebiotic interventions. Different effects on various mediators of the gut-brain axis have been demonstrated using several probiotics such as *Bifidobacterium infantis* which resulted in a decrease in pro-inflammatory cytokines in maternally deprived offspring rats. Additionally, the chronic treatment with *L. rhamnosus* induced region-dependent alterations in $GABA_{B1b}$ mRNA in the brain with increases in cortical regions in comparison with control-fed mice. These results among others showed that probiotics influence brain neurochemistry **(Saulnier *et al.*, 2013)**.

2. 3 Gut-brain communication pathways:

The gut and the brain communicate bidirectionally in multiple ways (direct and indirect) through neural, immune, endocrine and systemic pathways as shown in the figure bellow (**Figure 3**). Thereby, any signal (neurotransmitters, cytokines, hormones…) generated in the gut may be recognized by the brain, and *vice versa*.

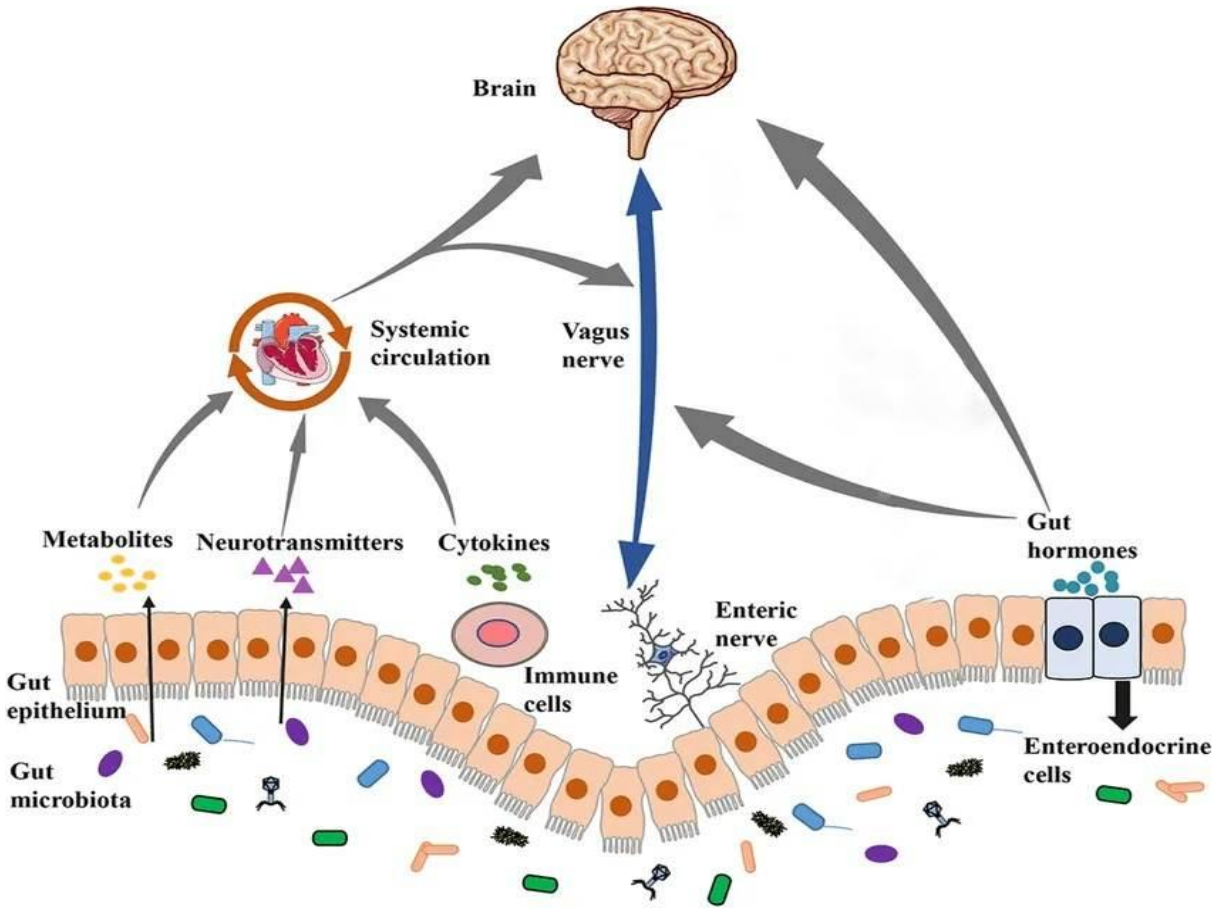

Figure3:Communication pathways of the microbiota-gut-brain axis, the crosstalk of the microbiota-gut-brain axis mainly comprised of four modules: metabolic, neural, immune, and endocrine signaling pathways **(Lin *et al.*, 2020)**.

Few major mechanisms mediating the effects of the gut microbiota on the brain have been identified as shown in **figure 4**. Among these are the activation of the vagus nerve, the immune system, the production of metabolites such as short-chain fatty acids (SCFAs) and vitamins, also the generation of compounds with neuroactive properties including serotonine , Gamma-aminobutyric acid (GABA) and more **(Averina et al. 2020)**.

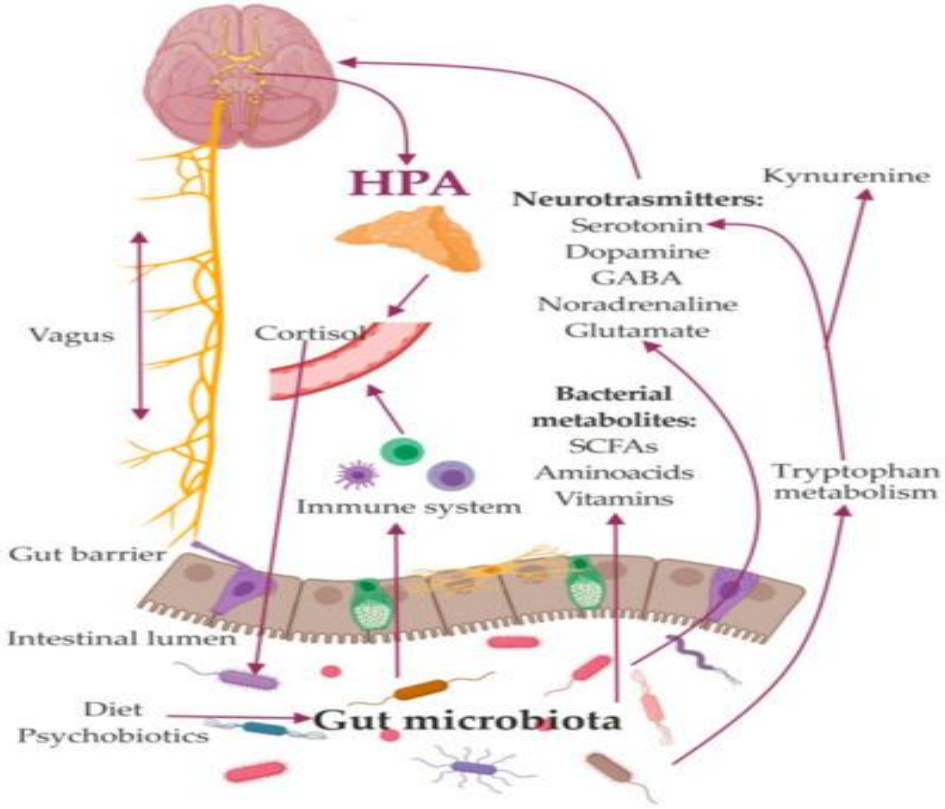

Figure 04: Schematic image of the role of the gut microbiome in the gut-brain axis. **(Averina *et al.*, 2020)**

2. 3. 1Immune-mediated inflammatory pathway:

The immune-mediated inflammatory pathway is a complex network of processes taking place in the body in response to infections, responsible for detecting and eliminating foreign invaders (bacteria, viruses, and other pathogens). Several types mediators are involved in this pathway, including cytokines, chemokines, leukocytes, and antibodies which are produced and released by various immune cells in response to injury.

Research have shown that alterations in the gut microbiota composition can lead to the dysregulation of the immune pathway and contribute to the development of inflammatory diseases. Many investigations were conducted highlighting the immune-mediated pathway between the gut and the brain. A study has shown that

- TH17 cells are activated by the gut microbiota and likely to be associated with certain pathologies such as autoimmune diseases. In fact, these cells are characterized by the secretion of IL-17A, IL-17F and IL-22 which are responsible

for IgA secretion, CD4+ memory , T cell differentiation and anti-*Staphylococcus aureus* function **(Hirota *et al*., 2013)**.

- It is noteworthy that interactions between the microbiota and the immune system predominantly occur in the hippocampus. Indeed, the gut microbiota produces a diverse range of pathogen-associated molecular patterns (PAMPs), including various components like lipopolysaccharides (LPS) and peptidoglycan (PGN). These PAMPs are released within the gut, enter the bloodstream, and engage with pattern recognition receptors (PRRs). Among these PRRs, Toll-like receptors, which are stimulated by LPS, play a crucial role in regulating hippocampal neurogenesis **(Rolls *et al*., 2007)**.

2. 3. 2 Neuronal pathway: *via* the innervation of the vagus nerve:

The vagus nerve (VN) is the longest nerve of the organism and a major component of the parasympathetic nervous system which constitutes the autonomic nervous system (ANS) with the sympathetic nervous system **(Bonaz *et al*., 2017)**.

One of the key component of the neuro-immune and brain-gut axis communication is the Vagus Nerve (VN), a mixed nerve with 80 % afferent and 20 % efferent fibers, through a bidirectional communication between the brain and the gastrointestinal tract **(Bonaz *et al*., 2017)**. The gut microbiota influences the CNS via the VN by transmitting gut microbiome signals from the luminal environment to the brain and *vice versa* **(Morais *et al*., 2021)**.

Disturbances in the VN can lead to CNS dysfunction (mood disorders, neurodegenerative diseases) or gastrointestinal pathologies (inflammatory bowel diseases, irritable bowel syndrome) **(Ma et al., 2019)**.

Furthermore, the vagus nerve has the ability to perceive signals from the microbiota through direct means. For example, certain compounds produced by the microbiota, such as short-chain fatty acids (SCFAs), can activate vagal afferent fibers through diverse mechanisms depending on the specific SCFA involved. Additionally, oleate, which is a long fatty acid, can impact vagal afferents through a mechanism mediated by acetylcholecystokinin (CCK). When oleate is present in the digestive system, it stimulates the release of CCK, a hormone produced by enteroendocrine cells in the small intestine. CCK than exerts various physiological effects, including the regulation of food intake and the modulation of communication between the gut and the brain **(Bonaz *et al*., 2018)**.

2. 3. 3 *Via* Neurotransmitters:

Monoamines neurotransmitters such as serotonine, glutamate , dopamine and gamma-aminobutyric acid (GABA) among others, are not only synthesized in neural cells, but also produced within the gastrointestinal system as shown in **figure 4 (Mittal *et al.*, 2017)**. They have been shown to play a major role in controlling and maintaining homeostasis within the gut system in terms of nutrient absorption, blood flow, local immune system function, and overall gut motility **(Mittal *et al.*, 2017)**.

2. 3. 4 *Via* microbial metabolites:

The gut microbiota metabolizes dietary components and produces a wide range of small molecules called microbial metabolites. Many of them have been identified as important signaling molecules that can influence the gut-brain axis:

2. 3. 4. 1 Short-chain fatty acids (SCFAs):

SCFAs are among the most widely studied microbial metabolites. They represent the main products derived from the fermentation of dietary fibers induced by commensal microbes. SCFAs are produced in the colon, mainly by *Firmicutes* and *Bacteroidete* **(Banfi *et al.*, 2021)**, include acetate, propionate, and butyrate and others .they have been shown to affect neuronal signaling, regulate intestinal permeability, promote the development of regulatory immune cells, and have anti-inflammatory effects **(Park *et al.*, 2021)**. Furthermore, they have the ability to directly or indirectly impact brain functions and behavior, notably through the modulation of neurotransmitters. SCFAs can influence the production and release of neurotransmitters in the brain, including serotonin, dopamine. These neurotransmitters are vital for regulating mood, cognition, and behavior **(Park *et al.*, 2021)**.

2. 3. 4. 2 Bile acids:

BAs are synthesized from cholesterol in the liver via oxidation catalyzed by cytochromes P450 (CYPs) and conjugation catalyzed by bile acid-CoA synthetase (BACS) and bile acid-CoA: amino acid N-acyltransferase (BAAT) **(Cai *et al.*, 2022)**. About 5–10% of BAs are secreted into the colon where they are mainly biotransformed by the gut microbiota or excreted into feces **(Cai *et al.*, 2022)**.

Gut microbiota and its BAs metabolites interact with the host and help maintain intestinal homeostasis through different BA receptors and cell signaling pathways **(Cai *et al.*, 2022)**. Bile acids stimulate the nuclear receptor farnesoid X receptor (FXR) in the ileum, the final section of the small intestine **(Mayer *et al.*, 2022)**. FXR plays a critical role in regulating BAs metabolism and maintaining homeostasis. Activation of FXR leads to the production of fibroblast growth factor 19 (FGF19), primarily synthesized in the ileum **(Mayer *et al.*, 2022)**. FGF19 function as an endocrine hormone, specifically involved in the control of BA synthesis and metabolism. Following FXR activation by BAs, FGF19 is released into the bloodstream and enters systemic circulation. It has then the ability to cross the blood-brain barrier and reach the arcuate nucleus of the hypothalamus **(Mayer *et al.*, 2022)**. This pivotal brain region is responsible for regulating various physiological processes, including energy balance, metabolism, and hormone secretion. Upon reaching the hypothalamus, FGF19 binds to its specific receptors in the arcuate nucleus, initiating signaling pathways that contribute to the regulation of food intake, energy expenditure, and glucose metabolism (**Mayer *et al.*, 2022)**.

2. 3. 4. 3 Tryptophan metabolites:

The essential amino acid tryptophan contributes to the normal growth and health of both animals and humans and, importantly, exerts modulatory functions at multiple levels of the GBA **(Gao *et al.*, 2020)**. Moreover, products of the tryptophan metabolism, such as serotonin, kynurenines, tryptamine, and indolic compounds, have profound effects on the interaction between gut microbiota and the GBA **(Gao *et al.*, 2020)**.

The gut microbiota produces a wide and diverse array of tryptophan metabolites, which are able to signal locally to the intestinal mucosa and also to distant organs, including the brain **(Gao *et al.*, 2020)**. This points to the crucial role of microbial tryptophan metabolites in communication between gut microbiota and the CNS **(Gao *et al.*, 2020)**.

Therefore the potential role of tryptophan metabolism in the gut microbiota-brain axis is by manipulating gut microbiota composition and metabolism by various ways (e.g., antibiotics and probiotics) also it contributes to the shifts in the central tryptophan metabolism between serotonin synthesis and tryptophan degradation pathways, which thereby influence the brain function and behaviors **(Gao *et al.*, 2020)**.

The major routes of tryptophan metabolism, including serotonin synthesis, the kynurenine pathway, and microbial degradation pathways as shown in the **figure 5**, are differentially affected in diseases, such as depression **(Gao *et al.*, 2020)**.

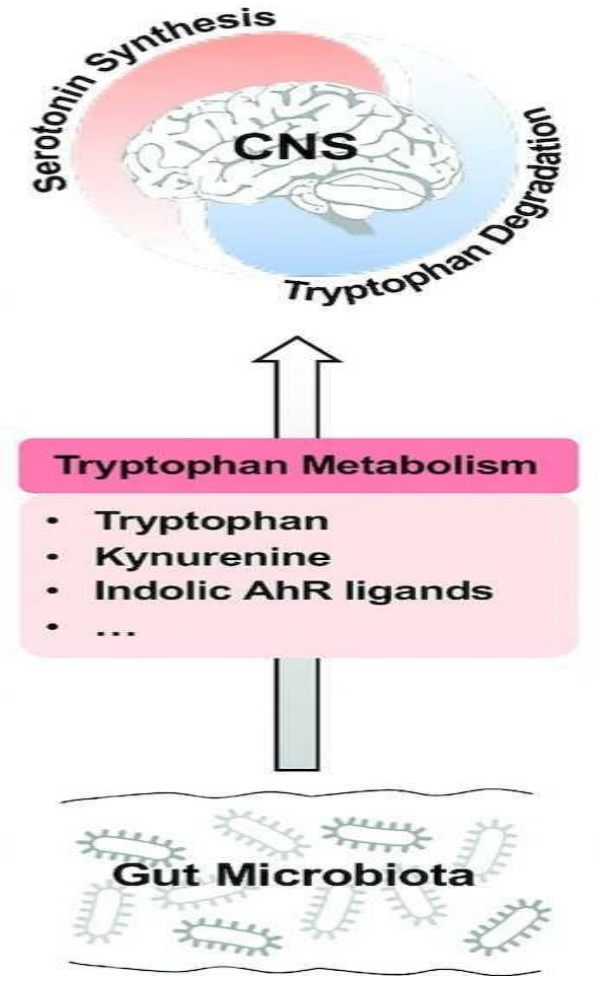

Figure 5 : The potential role of tryptophan metabolism in the gut microbiota-brain (Gao *et al.*, 2020)

2. 3. 5 Via the Hormonal pathways:

Among the diverse pathways by which the gut can signal the brain, the endocrine system seems to play a crucial role, as it is capable of modulating not only other endocrine functions, but also the neural and immune systems **(Lach *et al.*, 2018)**.

The gut endocrine system is comprised of gut peptides and other signaling molecules (i.e., serotonin), which are released by different types of enteroendocrine cells along the GI tract in response to food intake, particularly after ingestion of carbohydrates and fats **(Lach *et al.*, 2018)**. These peptides participate in gut-to-brain communication **(Lach *et al.*, 2018)**.

They may be envisaged to orchestrate the molecular, functional, behavioral, and autonomic reactions that take place in response to alterations of the gut microbial community **(Lach *et al*., 2018)**.

3 Gut-brain axis and CNS:

The gut-brain axis is known to be involved in regulating many physiological, functional and tissue processes as described below.

3. 1 Neurogenesis:

Neurogenesisis the process of generating new neurons from undifferentiated neural precursors. It contributes to plasticity-related processes such as memory, cognition, mood, and sensory function **(Azari *et al*., 2016)**. The gut microbiota has been shown to contribute significantly to neurogenesis and the production of neurotrophins, which regulate the development of the vertebrate nervous system by activating two different classes of receptors; the Trk family of tyrosine kinases receptors and p75NTR, member of the TNF receptor superfamily **(Huang *et al*.,2001)**.

3. 2 Microglia:

These are the primary resident immune cells in the CNS, responsible for pathogen surveillance and immune protection. They also maintain an optimal number of synapses, play an important role in the construction and shaping of neural circuitry during postnatal development, which has implications in cognitive function and social behavior **(Morais *et al*., 2021)**.

Microglia can initiate pro- or anti-inflammatory signaling cascades. The activation of pro-inflammatory signaling pathways causes microglia to release pro-inflammatory cytokines such as IL-6, IL-12, IL-1β, and TNF-α, but also nitric oxide and reactive oxygen substances in order to suppress and resist invading pathogens **(Roser *et al*., 2017)**. However the activation of anti-inflammatory pathways enables microglia to attenuate inflammation by triggering the release of anti-inflammatory cytokines (IL-4, IL-10, TGF-β) and neurotrophic factors that prevent the development of chronic inflammation, which allow microglia to maintain their neuroprotective and wound-healing properties, thereby repair the caused damage by the pro-inflammatory response **(Roser *et al*., 2017)**.

Despite the many unanswered questions concerning the intersection between gut microbiota and microglial physiology, there is evidence that pathways that collectively integrate the gut–brain axis influence microglial function in both homeostatic and disease conditions **(Roser *et al.*, 2017)**. Recent studies showed that microglia are sensitive to factors produced by the gut microbiota, striking differences in their structure and function both at the genetic and morphological level, which suggests their involvement in psychiatric and neurodegenerative disorders **(Abdel-Haq *et al.*, 2019)**.

3. 3 Astrocytes:

They are a subtype of glial cells in the central nervous system that participate in the implantation of the blood-brain barrier and its function **(Abbott, 2002)**. Astrocytes play a role of interface between microglia and neurons, and exert vital effects on synapse formation during development and adult neurogenesis **(Song *et al.*, 2002)**.

Astrocytes possess multiple receptors, activated by their specific neurotransmitters (eg., glutamate, serotonin), ATP, and cytokines known to contribute to the dysfunction of the brain under pathological conditions **(Chung *et al.*, 2015)**. Astrocytes abnormalities have a crucial role in the neuroinflammation pathophysiology, and have been regularly observed in many neural disorders , such as neurodegenerative diseases(Alzheimer, Parkinson's disease , epilepsy) as well as psychiatric ones (major depressive disease, autism spectrum disorders).

Gut microbiota factors are among the most potent modulators of astrocytic count number, morphology, activation and functions. The microbiota modulation of astrocytes' activity is supposed to occur through the gut-brain axis, *via* the three pathways (immune, neuronal and neuroendocrine) **(Zhao *et al.*, 2021)**.

3. 4 Blood-brain-barriers:

The blood–brain barrier (BBB) is an extension of the neural microvasculature, composed of a network of endothelial cells sealed with tight junctions. This physiological barrier helps to maintain CNS homeostasis by regulating the transport of nutrients, critical gases (O2 and CO2), protecting the brain from pathogens and hydrophilic molecules contained in the cerebral spinal fluid. However, BBB can be disrupted, which alters its integrity and therefore its functions **(Dono *et al.*, 2022)**.

4 Brain tumors:

Also called central nervous system tumors, brain tumors are characterized by a growth of abnormal cells in the brain tissues. They can be benign or malignant **(Louis *et al.*, 2007)**. Brain tumors are generally classified according to their origin. Actually, they can be either primary, which means arise in the brain only, or secondary (metastasis), denoting that they appear elsewhere in the body and spread to the brain **(Whitfield *et al.*, 2022)**. On another hand brain tumors can be classified based on their localization as shown in **figure 6**.

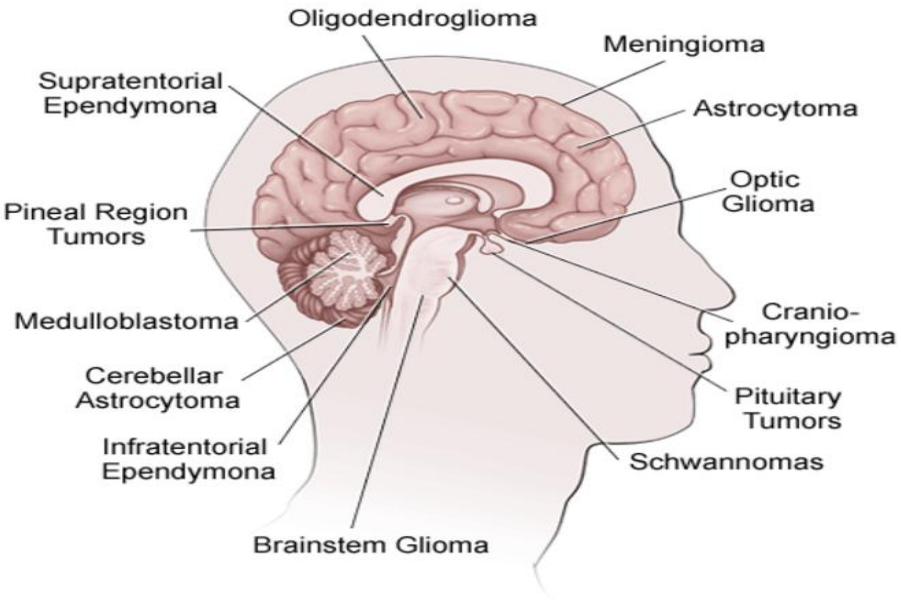

Figure 6: Types of brain tumor according to their localization. Brain tumors can affect different regions of the brain such as the meninges, astrocytes, Schwann cells *etc* **(Abiodun Ogunleke, 2019)**

4. 1 Classification of brain tumors:

Before 2021, brain tumors were classified according to the 2007 World Health Organization (WHO) classification of tumors of the central nervous system which was largely based on histological features **(Louis *et al.*, 2007)** (**Table II**). This system was updated in 2016. For the first time, the WHO classification of CNS tumors incorporated molecular parameters such as TP53, EGF and implication of IDH in addition to histology to define many tumor entities **(Louis *et al.*, 2016)**. In 2021, the fifth edition of this classification was published. In this latest edition, new types and subtypes were introduced and the criteria for histomolecular diagnosis and grading are refined, particularly for diffuse gliomas. The recognition of "pediatric subtype" diffuse gliomas (low- or high-

grade) represents a major improvement in the classification which will lead to a better management of brain tumor patients **(Louis *et al.*, 2021)**.

Table II: classification of brain tumors according to their degree of malignancy (Kim *et al.*, 2022)

Grade	*Tumor types*	*Characteristics*
Grade I	• Craniopharyngioma • Ganglioglioma • Gangliocytoma	Least malignant brain tumor, non infiltrative, it can be treated through surgery alone.
Grade II	• Pineocytoma • "Diffuse" astrocytoma • Pure oligodendroglioma	A slight infiltrative brain tumor which is relatively slow growing can recur as higher grade.
Grade III	• Anaplastic ependymoma • Anaplastic astrocytoma • Anaplastic oligodendrogliomal	Malignant brain tumor, infiltrative and tend to recur as higher grade.
Grade IV	• Glioblastoma multiforme • Medulloblastoma • Ependymoblastoma	Most malignant type, rapidly growing and aggressive and widely infiltrative, it often shows a tendency for recurrence to a necrosis.

4. 2 Epidemiology of brain tumors:

According to the World Health Organization (WHO), brain tumors rank 20th in terms of incidence, and 13th in terms of mortality, they represent the most frequent cancer pathology after ovarian cancer **(GLOBOCAN, 2020).**

In Algeria, brain tumors are among the 10 most common tumors, they rank 10th in terms of incidence and 7th in terms of mortality. With a sex ratio (Male/Female) of 4.4:3.8, they are more frequent in males **(GLOBOCAN, 2020)**.

A retrospective epidemiological study was carried out in Bejaia's Hospital at the neurosurgical department from 2012 to 2022 which a total sampling of more than 700 cases of various brain tumors. The results highlight an incidence rate 7.16 per 100,000 individuals, which is three times higher, with relatively early median age onset of 47 years (58 for Europe and America) **(Khireddine *et al.*, 2023)**.

4. 3 Biomarkers of brain tumors:

Biomarkers can be molecules, genetic mutations, or any other biological parameters, which once measured or analyzed, provide information on a biological, physiological or pathological process.

The development of a tumor is a complex process leading to a number of biochemical and molecular changes. Using biomarkers for detecting these changes is a promising technique for early detection **(Jelski *et al.*, 2021)**. They are also used to represent the tumor status of a patient as shown in **table III**.

Studies have shown that a significant dysbiosis in the structure and function of gut microbiota is observed in brain tumor patients. Moreover, a microbial panel of *Fusobacterium, Akkermansia, Escherichia/Shigella, Lachnospira, Agathobacter,* and *Bifidobacterium* could be used as biomarkers for the diagnosis and/or prognosis of brain tumor patients which is a promising field for clinical application **(Jiang *et al*., 2022)**.

Table III: The biomarkers of brain tumors used in clinic.

Tumor markers	*Clinical application*	*References*
IDH enzyme mutation	Patients with IDH-mutated gliomas generally have a better prognosis compared to those with IDH-wild type tumors	**(Siegal., 2015)**
1p19q co-deletion	Patients with tumors having 1p19q co-deletion generally have a better prognosis	**(Siegal., 2015)**
EGFR mutation	EGFRvIII expression has been demonstrated to confer a worse prognosis than EGFR wild-type expression alone	**(Yoshimoto *et al*., 2012)**

Chapter II

Research Methodology

Research Methodology:

This study provides an overview on the literature concerning the relationship between gut microbiota and brain tumors. Relevant information was collected using various scientific search engines, such as Pubmed (NCBI) and Google Scholar.

For this purpose, multiple key words were used as shown in the following table (**Table IV**).

Table IV: Keywords used in the research.

Keywords used separately	*Various combinations of keywords*	*Keywords that didn't give refined results*
• Gut microbiota • Gut microbiota composition • Dysbiosis • *Firmicutes* • *Actinobacteria* • *Bacteroidete* • Blood brain barrier • Brain tumors • Biomarkers • Foxp3 • Short Chain Fatty Acids • Immunotherapy • PD-1/ PD-L1	• Gut microbiota **AND** Dysbiosis • Gut microbiota **AND** Brain Tumors • Gut microbiota Dysbiosis **AND** Brain Tumors • classification **AND** Brain Tumors • Epidemiology **AND** Brain Tumors • Biomarker **AND** Brain Tumors • Immune state **AND** Microbiome **AND** Brain Tumors • Foxp3 **AND** Brain Tumors • Metabolites **AND** Gut microbiota **AND** Brain Tumors • Short Chain Fatty Acids **AND** Brain Tumors	• Astrocytoma • Schwannomas • Oligodendroglioma • Biomarkers **AND** Gut microbiota • Disruption **AND** Blood Brain Barrier **AND** Gut Microbiota **AND** Brain Tumors • Fungi **AND** Brain Tumors

Keywords used separately	*Various combinations of keywords*	*Keywords that didn't give refined results*
	• Blood Brain Barrier **AND** Gut Microbiota • Disruption **AND** Blood Brain Barrier **AND** Gut Microbiota **AND** Brain Tumors • Immunotherapy **AND** Brain Tumors • Immunotherapy **AND** Brain Tumors • PD-1/ PD-L1 **AND** Brain Tumors	

Chapter III

Results and Discussion

Studies Highlights

The collected manuscripts were assessed for relevance based on their titles and abstracts, resulting in the selection of seven research and review articles

Table V: The main findings of the selected articles.

References	*Brain tumor type*	*Study Model*	*Main Findings*
(Fan *et al*., 2022)	Glioma	Mice glioblastoma (cell line implanted in mice)	Gut microbiome dysbiosis may promote glioma growth by downregulating Foxp3
(Yingying Lyu *et al*., 2022)	Glioma	Mice	Short Chain Fatty Acids can cause inhibition of NF-κB and TNF-α in the brain
(Braniste *et al*., 2014) **(Sarkaria et al., 2018)**	Glioma	Mice	Blood brain barrier can be disrupted due to a gut microbiota dysbiosis
(Kory J. Dees *et al*., 2021)	Glioma	Humanized microbiome mice model	Human gut microbiota can modulate the response to immunotherapy in a mouse model of glioma.
(Fan *et al*., 2022) **(Jiang *et al*., 2022)** **(Li *et al*., 2022)**	Glioma Meningioma/Glioma Meningioma/Glioma	Mice Human (n=100) Human (n=158)	Alterations in the composition of the fecal microbiota in Brain Tumor Patients

1 Alterations in the Composition of the Fecal Microbiota in Brain Tumor Patients:

Emerging evidence suggests that the gut microbiota plays a crucial role in modulating systemic inflammation, immune responses, and even the central nervous system. Therefore, investigating the alterations in the fecal microbiota composition in brain tumor patients holds promise for understanding potential connections between the gut

microbiome and brain health. Gut microbiota is able to modify mediators' levels in the brain and their influence on cell proliferation in physiological condition and tumor glioma cells. Therefore, microbiome is considered as a key determinant in brain tumor progression **(D'Alessandro *et al.*, 2021)**. Based on the fact that the GM's patients with benign and malignant tumors may differ significantly, many studies have aimed to explore the potential relationship between the diversity of gut microbiota in healthy controls and brain tumor patients. This hypothesis was previously confirmed in animal studies, mainly focusing on malignant gliomas, followed by human studies. Findings across all levels of diversity tend towards the same outcomes.

Fan and collaborators (2022) investigated the effects of glioma growth on gut microbiome in mice and studied the effects of GM dysbiosis on glioma development using a 16s rDNA gene sequencing method. First, to evaluate whether glioma growth can change the GM structure, they implanted GL261-Luc cells (murine glioma cell line) into healthy C57BL/6 mice to establish glioma models. They then compared the 16s rDNA in fecal samples before tumor implantation, after 14 days of tumor growth, and fecal samples after 21 days of tumor progression.

Taxa analysis revealed that glioma development induced structural changes in the gut microbiome of mice. Before tumor cells implantation (in the healthy controls) the GM of mice was predominantly composed of *Bacteroidetes*, *Firmicutes*, and *Actinobacteria*. Notably, the abundance of *Bacteroidia* and *Actinobacteria* in mice GM decreased as the glioma develop, while the abundance of *Firmicutes* increased **(Fan *et al.*, 2022)**. Consequently The role of the gut microbiota in the glioma-bearing mice model has been established, indicating that the composition of intestinal flora may significantly differ between healthy individuals and patients with and malignant tumors **(Fan *et al.*, 2022).** However, the correlations and precise mechanisms by which these microbes act on brain tumors progression remain unclear.

Therefore, the first human study conducted by Jiang and collaborators (2022) took place in order to investigate the correlation between GM, benign and malignant brain tumors. They recruited 59 patients, including 32 with meningioma and 27 with malignant glioma, and 41 healthy subjects, extracted microbial RNA from their fecal samples, and run them through 16S rRNA gene sequence analysis.

The study showed, profound microbial composition changes in both meningioma and glioma patients. These findings were concordant with the outcomes of the previous mice experiments.

Indeed, in the healthy control groups, at the phylum level, the most abundant gut microbes were *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, and *Fusobacteria*. Although, at the genus level, the most prevalent microbes were *Bacteroides*, *Prevotella*, *Faecalibacterium*, *Agathobacter*, *Megamonas*, and *Lachnospira*.

Regarding the meningioma group, the most common gut microbes at the phylum level were *Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria,* and *Verrucomicrobiota*, while at the genus level were *Bacteroides, Prevotella, Faecalibacterium, Escherichia/Shigella, Megamonas*, and *Roseburia*.

As for the glioma group, the results showed that, at the phylum level, the most common microbes were *Bacteroidetes, Firmicutes, Proteobacteria, Fusobacteria, Verrucomicrobiota*, and *Actinobacteria*. Whereas, the most prevalent gut microbes at the genus level were *Bacteroides, Prevotella, Faecalibacterium, Phascolarctobacterium,* and *Escherichia/Shigella* **(Jiang *et al.*, 2022)**.

Finally, another human study, involving a larger sample size, was conducted **(Li *et al.*, 2022)**. The inquiry aimed to investigate potential differences in the gut microbiota associated with various brain tumors. A total of 158 participants were recruited, including 101 patients with brain tumors and 57 healthy controls. The brain tumors were categorized into benign tumors (primarily meningiomas and pituitary tumors, totaling 65 cases) and malignant tumors (gliomas and metastatic brain tumors, totaling 36 cases).

The findings are inlined with the previous ones, demonstrating significant alterations in the gut microbiota compositions associated with brain tumors. Notably, there was an increase in the abundance of pathogenic bacteria. Moreover, the data revealed substantially lower richness and evenness in the microbial ecosystem of patients with brain tumors compared to that of healthy controls. This decrease in microbial diversity in the fecal microbiota of brain tumor patients, compared to healthy individuals is associated with dysbiosis and altered microbial functions. In all studies cited previously, At the phylum level, the *Firmicutes* and *Bacteroidetes* were the dominant flora of each group , while the

Firmicutes to *Bacteroidetes* ratio (F/B) decreased in brain tumors **(Jiang *et al.*, 2022)**. Low F/B was found to decrease circulating short-chain fatty acids (SCFAs) and induce metabolic dysfunction. Changes at the genus levels were more complex **(Jiang *et al.*,2022)**. Indeed, reducing beneficial bacteria may be a risk factor for brain tumors, so in addition to exploring the underlying pathogens, studies also evaluated the low-abundance of beneficial bacteria in brain tumor patients. In fact, Jiang and collaborators study pointed out the decrease of both *Lachnospira* and *Agathobacter* genera in the unhealthy brain patients that may possess anti-tumor activity through butyric acid production. These anaerobic bacteria are the primary producers of butyrate, which plays a crucial role in gut physiology. Additionally, it is linked to the regulation of the intestinal cell life cycle and possesses the ability to inhibit pathogen invasion, impede tumor advancement, and regulate immune responses in the CNS **(Jiang *et al.*, 2022)**.

On another hand, the relationship between carcinogenic gut bacteria and brain tumors is an area of active research and is not yet fully understood. Therefore, the direct relationship between them is still being explored. Pathogenic gut bacteria are known to produce various metabolites and toxins that can have systemic effects on the body, including inflammation and immune system modulation. Chronic inflammation and immune dysregulation have been implicated in tumor development and progression in various parts of the body, including the brain. Jiang and collaborators study showed the presence of "*Escherichia/Shigella*", in meningioma patients, that has already been reported to promote chronic neurological inflammation by neurotoxicity and consequently brain tumors.

The main limitation of these studies is the "small" sample size, which may restrict the generalizability of the findings to a larger population. It also reduces the statistical power and increases the risk of chance findings. Also, these studies only include patients with meningioma and glioma, as these are the most prevalent benign and malignant brain tumors, respectively. Enrolling more subtypes and samples is than necessary to reach more credible conclusions.

All these results indicate an undirect effect of the gut microbiota on the brain tumors. According to Newton's third law of motion, often referred to as the law of action and reaction which states that for every action, there is an equal and opposite reaction. We hypothesize that if the gut exerts a "force" on the brain, then probably the brain exerts an equal magnitude but opposite in direction and force on the gut. Further investigation is

warranted to explore the bidirectional effect mentioned above. Additionally, a more comprehensive molecular study is necessary to deepen our understanding of the underlying mechanisms and provide additional insights.

2 Immune state and microbiome in brain tumor:

In recent years the relationship between the immune system, gut microbiota and brain tumors has captivated attention in scientific research. Various studies have shown that a dysbiosis in the intestinal flora can lead to an alteration of immune responses that can promote the development of brain tumors or maybes their initiation.

2. 1 Modulation of systemic immune response:

Foxp3 Downregulation:

Forkhead box P3 (FoxP3) is a member of forkhead winged helix family transcription factors; it plays a dual role as a transcription activator and repressor. FoxP3 expression is essential for the differentiation of CD4+/CD25+ regulatory T cells (Tregs) which are critically important for the prevention of autoimmune diseases. Tumors are often populated by $FoxP3^+$ T cells which regulate anti-tumor immunity **(Janka Held-Feindt *and al.*, 2012)**.

In a previously cited study, conducted by Fan and collaborators, the authors explored the effect of gut microbiome dysbiosis, induced by antibiotic, on the glioma microenvironment in mouse brain tissues. Immunohistochemical results showed that Foxp3 expression was lower in the ABT group (Anti Biotic Treated group) than in the Non-ABT group. These results suggest that gut microbiome dysbiosis may promote glioma growth by downregulating Foxp3 expression in the glioma microenvironment. Hence, a balanced environment of GM can upregulate the expression of Foxp3 in the brain, which will result in a slowdown of glioma development **(Fan *et al.*, 2022)**.

Furthermore, Foxp3 can slowdown the progression of brain tumors by facilitating apoptosis. In a study run by Janka Held-Feindt and collaborators using quantitative RT-PCR, immunohistochemistry and Fluorescence-Activated Cell Sorting (FACS) analysis on human glioma cells obtained from surgical dissected human glioma samples (11 male patients and six females). The results revealed that FoxP3 mRNA was present in all analyzed glioblastoma homogenates. Moreover, after exposure of glioma cell lines to

chemotherapeutic drugs, expression of FoxP3 was significantly enhanced. Finally, overexpression of FoxP3 in glioma cell lines considerably promoted apoptotic damage of nuclei and DNA fragmentation, revealing that overexpression of Foxp3 in glioma cells, facilitates apoptosis and increases cell sensitivity to apoptotic stimuli **(Janka Held-Feindt *et al.*, 2012)**.

Metabolites influence on immune cells:

Metabolites of gut microbiota alter the behavior of immune cells such as microglia in the brain and regulate astrocytes activity either to promote or prevent inflammation **(Yingying Lyu *et al.*, 2021)**.

SCFAs can affect NFκB function in cancer and immune cells. This transcription factor plays a major role in the production of inflammatory cytokines, such as IL-6 and IL-8, which in return play an essential role in the regulation of tumor microenviroment. It's noteworthy that proinflammatory cytokines were found to promote the initiation and progression of brain tumors. In cancer cells, alterations of the NFκB pathway caused by high levels of IL-6 activate survival genes such as STAT3, a signal transducer and activator transcription factor that can promote tumor growth, invasion and enhance tumor aggressiveness **(Yingying Lyu *et al.*, 2021)**.

Moreover, some of the SCFAs can enter the CNS through the blood circulation, especially if the blood–brain barrier (BBB) permeability is high. They can influence the polarization of microglial cells through epigenetic modifications **(Yingying Lyu *et al.*, 2021)**. Its noteworthy that acetate along with glucose are the most abundant nutrients in brain, they are wildly up taken by tumor cells, and participate in the TCA cycle (The Citric Acid cycle) to impact acetyl-CoA production and produce energy **(Yingying Lyu *et al.*, 2021)**. In return, acetyl-CoA promote cellular signaling of the epidermal growth factor receptor vIII (EGFRvIII) an EGFR mutant occurring frequently in glioblastoma, through activation of mechanistic target of rapamycin complex 2 (Mtorc2) by acetylation of its core component Rictor. In consequence, this mechanism will increase the metabolism of the brain tumor and thereby promote its progression **(Masui K *et al.*, 2015)**.

2. 2Disruption of the Blood brain barrier:

Blood brain barrier (BBB) as described previously is a physiological barrier that protects the brain from pathogens, toxins and other harmful molecules.

In 2014, Braniste and collaborators conducted a study to evaluate the impact of the intestinal microbiota on the maintenance of the BBB integrity in a germ-free (GF) mouse model. The integrity of the BBB was appraised using functional permeability assays and by determining the status of tight junctions. In order to assess these features the authors used three groups of mice, a group of germ-free adult mice as a control, another one colonized with fecal samples from pathogen-free mice, a group treated with bacterial strains that produce SCFAs and a last group of germ-mice treated with the bacterial metabolite sodium butyrate (BMSB) **(Braniste *et al*., 2014)**.

The results show that gut microbiome influences the development and maintenance of tight junctions of the BBB. Indeed, GF mice, who lack a normal microbiome, have significantly higher levels of BBB permeability. While, microbial colonized GF mice and mice treated with SCFAs-producing bacterial strains or BMSB show a decrease in the BBB permeability and an increase in the expression of tight junction proteins such as occluding and claudin-5 **(Braniste *et al*., 2014)**.

Moreover BBB may be disrupted in brain tumors, in both primary and metastatic type **(Mo *et al.*, 2021)**. This disruption may promote the progression and development of brain tumors by altering the microenvironment of the brain. On another hand, this disruption can be helpful to treat brain tumors by allowing the crossing of therapeutics drugs, in particular lipophilic molecules, from the blood to the brain.

Although, not all types of brain tumors have a disrupted blood brain barrier. As a matter of fact, a study conducted by Sarkaria and collaborators in 2018 showed that all glioblastomas have clinically significant regions of tumor with an intact BBB (**Sarkaria *et al*., 2018**). Nevertheless, this study did not take in account the presence or not of a dysbiosis.

2. 3 Modulation of immunotherapy:

Immunotherapy has been emerging as a promising field in the treatment of tumoral pathologies. Various immune checkpoints inhibitors have performed well in several

cancers and shown remarkable progress in both pre-clinic and clinical trials **(Yang *et al.*, 2022)**.

Although immunotherapy showed promising results in brain tumor preclinical mouse models such GBM's, the demonstration of their efficacy in treating humans was unsuccessful. Dees and collaborators addressed this problem by conducting a study where they developed a novel humanized microbiome model to explore the response of human gut microbiota to immunotherapy in a preclinical mouse model of GBM. They used five healthy human donors for fecal transplantation of gnotobiotic mice (germ-free mice model). After stabilization of the transplanted microbiomes, the mice were bred to generate five independent humanized mouse lines (HuM1 to HuM5) **(Dees *et al.*, 2021)**.

Analysis of shotgun metagenomic sequencing data from fecal samples revealed a unique microbiome with significant differences in diversity and microbial composition among HuM1 to HuM5 lines. Moreover, all HuM mouse lines were susceptible to GBM transplantation, and exhibited similar median survival ranging from 19 to 26 days **(Dees *et al.*, 2021)**.

Notably, HuM mouse lines responded differently to the immune checkpoint inhibitor anti-PD-1. This last one, prevents PD-1 receptors expressed on T cells from interacting with PD-L1, a protein present both on the surface of cancer cells and on the surface of healthy cells **(Han *et al.*, 2020)**. Consequently, anti-PD-1 avoids inhibition of immune cell activity and thus prevents the progression of brain tumors. Dees and collaborators study showed that HuM1, HuM4, and HuM5 mice are non-responsive to anti-PD-1, while HuM2 and HuM3 mice responded to the inhibitor and presented significantly increased survival compared to isotype controls. The non responsive mice are genetically identical to the HuM2 and HuM3 mice, and their difference lays in the diversity of the gut microbiome content. This indicates that the microbiome composition of HuM1, HuM4, and HuM5 leads to an inability of anti-PD-1 to boost an immune response to attack the stop tumor growth. Coincidentally, this complete resistance and failure of anti-PD-1 to decrease tumor growth and prolong survival is what is observed in GBM patients.

It would be interesting to explore how microbes affect immune cells of the gastrointestinal tract, thus, demonstrate how microbiota influence anti-tumor immune response. This could allow to explore new ways to enhance the efficacy of immunotherapy.

Conclusion and Future Prospects

In conclusion, this review indicates the important effect that gut microbiota has on the biology of brain. Indeed, these two components of our body are linked by the gut-brain-axis, in a bidirectional communication pathway which may play an important role in modulating the interaction between the intestine microbiota and brain physiology.

A dysregulation of the composition and function of the gut microbiota called a dysbiosis can promote the development of brain tumors. Metabolites produced by the intestinal flora such as short chain fatty acids can have a direct effect on the immune system, the blood brain barrier and consequently affect brain tumor cells. Also, the gut microbiota can modulate systemic inflammation and immune cell activation. This regulation of the tumor microenvironment enhances the development of brain tumors and alters the efficacy of immunotherapy.

However, there are still few grey areas that require further exploration. In order to better understand the complex relationship between the gut microbiota and the brain, it is recommended to carry out metagenomic studies of histological sections of brain tumors. Metagenomic is defined as a study of environmental microbial communities using a suite of genomic tools to directly access their genetic content. By conducting such studies, we can demonstrate effectively the impact of the microbiome on brain tumors and enhance our understanding of this impact.

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Abstract

The gut microbiota (GM), a complex and dynamic population of microorganisms that resides within the human gastrointestinal tract and has a significant impact on the host. There is growing evidence suggesting that GM may be implicated in neurological diseases. Therefore, ongoing research investigating the link between brain tumors and gut microbiota took place. While the exact mechanisms are not yet fully understood, some studies have suggested that the GM dysbiosis; referring to an imbalance in the composition or function of the microbial community that resides within the human gut, may play a role in the development or progression of brain tumors. Moreover, researches have shown that particular bacterial strains may produce compounds that could be involved in the development of these tumors. The GM has the potential to influence the immune system and inflammation, which may affect the growth and progression of tumors.

Keywords: Gut Microbiota, Dysbiosis, Brain tumor.

Résumé

Le microbiote intestinal (MI) est une population complexe et dynamique de micro-organismes qui réside dans le tractus gastro-intestinal humain et qui a un impact significatif sur l'hôte. De plus en plus d'éléments suggèrent que le microbiote intestinal pourrait être impliqué dans les maladies neurologiques. C'est pourquoi des recherches sont en cours sur le lien entre les tumeurs cérébrales et le microbiote intestinal. Bien que les mécanismes exacts ne soient pas encore totalement compris, certaines études ont suggéré que la dysbiose du microbiote, c'est-à-dire un déséquilibre dans la composition ou la fonction de la communauté microbienne qui réside dans l'intestin humain, pourrait jouer un rôle dans le développement ou la progression des tumeurs cérébrales. En outre, des recherches ont montré que des souches bactériennes particulières peuvent produire des composés qui pourraient également être impliqués dans le développement de ces tumeurs. Le MI a le potentiel d'influencer le système immunitaire et l'inflammation, ce qui peut avoir une incidence sur la croissance et la progression des tumeurs.

Mots clés : Microbiote intestinale, Dysbiose, Tumeurs cérébrales.