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The Gut–Brain Axis, Paving the Way to Brain Cancer

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Abstract

The gut-brain axis formed by blood and lymphatic vessels paves the way for microbiota to impact the brain. Bacterial populations in the gut are a good candidate for a nongenetic factor contributing substantively to brain tumor development and to the success of therapy. Specifically, suppression of the immune system and induction of inflammation by microbiota sustain proliferative signaling, limit cell death, and induce angiogenesis as well as invasiveness. In addition, altered microbial metabolites and their levels could stimulate cell proliferation. We propose here a novel gear model connecting these complex interdisciplinary fields. Our model may impact mechanistic studies of brain cancer and better treatment outcomes through precision oncology.

The Complex Role of Genetics, Immune State, and Microbiome in Brain Cancer Development

Tumors of the central nervous system (CNS) represent a major source of cancer-related deaths in adults and in children [1]. Studies of the molecular etiology of these devastating diseases have elucidated various genetic alterations involving cell survival and DNA repair pathways [2]. Rational targeted therapy to these pathways was not effective or showed only very mild improvement in survival [3]. In addition to tumor heterogeneity being a major obstacle to finding a common and effective treatment, during brain neoplasia there is a process of immune suppression, providing an environment that favors tumor growth [4–7]. While immunotherapy efforts are under way to disrupt these mechanisms and to turn the immune system against developing tumors [8], understanding how the immune suppression is initiated is a crucial step toward inhibiting tumorigenesis. We review here the possible impact of the gut–brain axis on the immune system state, inflammation, tumorigenicity, and response to treatment. Precision medicine taking into account the microbiome’s impact on immune suppression and treatment response would result in immune response activation and better response to treatment and would increase patient survival.

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Balanced Immune Function Is Important in Preventing the Establishment of Brain Cancer

The brain is presumably an immune-privileged organ due to the blood–brain barrier (BBB) [9]. The internal immune functions in the brain are modulated by microglial cells. Microglia can be polarized to a prodestruction (M1 microglia) or tissue-regenerating (M2 microglia) state. The immune system helper T (Th) cells are cytokine-producer T lymphocytes. Th1 cells produce proinflammatory cytokines whereas the Th2 type produce interleukins including interleukin-10 (IL10), which has an anti-inflammatory response [10]. In response to pathogens, microglia activate T cells and secrete proinflammatory cytokines including TNF α , IL6, and IL1 β [11]. Subsequently, to downregulate this reaction, T cells release cytokines including IL4 and IL13 to transform microglia from M1 to M2 [12]. Unregulated extensive tissue remodeling by activated microglia can lead to brain tumors [13]. The microglial/macrophage cytokine CSF1 and its receptor CSF1R are overexpressed in human high-grade gliomas [14]. It has been shown that, in glioblastomas, Th2 cytokines including IL6 and TGF β are strongly expressed. By contrast, Th1 cytokines including IL2 and IL12 are absent in glioblastoma tumors [15]. In the absence of a microbiota, microglial maturation is attenuated and their response to pathogens is limited [16]. Furthermore, some microglial impairment can be remedied by the administration of a microbiota [17].

During gliomagenesis, the BBB is broken and circulating immune cells, including T cells, B cells, macrophages, and myeloid-derived suppressor cells, cross the barrier [18]. The resulting bidirectional communication between immune cells and glioma cells creates an immunosuppressed microenvironment that promotes tumor survival and growth [19]. Glioma-associated microglia and macrophages are attracted to the tumor [20] and can be polarized into M2 cells, becoming tumor supportive and immunosuppressive [21]. Elevated M2 is associated with glioblastoma multiforme (GBM) [22] and inversely correlated with survival time [23]. Activated microglia secrete cytokines and growth factors that promote tumor cell growth and angiogenesis, such as IL10, EGF, and VEGF [24]. IL10 also inhibits T cell proliferation and confers an immunosuppressed state [25]. These cells fail to secrete proinflammatory cytokines (IL6, IL1 β , TNF α) and are thus incapable of activating a cytotoxic state in CD8⁺ T cells [26].

The immunosuppressive environment in glioma is further enhanced by elevated numbers of regulatory T cells (Tregs) [27] which produce high levels of IL10 and TGF β [28]. Tregs are believed to be a primary regulator of the immunosuppression present in the glioma microenvironment [29]. Moreover, Treg numbers are correlated with the WHO grade of the brain tumor [30], while depletion of Tregs in mouse glioma models improves survival [31].

Natural killer (NK) cells of the innate immune system can kill tumor cells without prior sensitization. The surveillance of cancer cells by the immune system is enhanced by IL2 and IFN α , which promote the growth and activation of T cells and NK cells [32]. By contrast, down-modulation of NK cell function in brain tumors could be in part due to elevated TGF β plasma levels [33]. It is noteworthy that the incidence of glioma is reduced in allergic and autoimmune conditions where there is constant activation of immunologic factors [34]. Therefore, balanced immune function as well as elimination of Tregs is important in

preventing the establishment of brain tumors. Appropriate activity of the microbiota and microglia reduces immune suppression and accordingly may be essential for the prevention and treatment of brain tumors.

Dysregulated Inflammation Cascade of Cytokines Promotes Tumor Development

Inflammation is a biological response to harmful stimuli such as pathogens, damaged cells, or irritants. For example, inflammation occurs as phagocytosing leukocytes are activated in response to damaged cells, and when dysregulated it paves the way to cancer [35]. This process sustains proliferative signaling, limits cell death, and induces angiogenesis as well as invasion, metastasis, and epithelial-to-mesenchymal transition (EMT) [36]. In humans, the proinflammatory cytokines IL1 β , IL6, IL8, IL12, GM-CSF, and TNF α are involved in brain tumor initiation and progression [37] and IL32 has inflammatory and angiogenic properties [38]. TNF α and IL6 directly affect tumor cell growth as well as survival, while IL6 is also immunosuppressive [39]. Activated inflammatory cells may also impact the tumor directly by the secretion of reactive oxygen species that induce DNA damage and by repressing mismatch-repair response genes [40]. The nuclear factor kappa B (NF κ B) family of transcription factors plays an essential role in the regulation of inflammatory responses, immune function, and malignant transformation [41,42]. Aberrations of the NF κ B pathway can activate survival genes in cancer cells [42,43]. In glioblastoma, IL6 induces NF κ B, resulting in STAT3 activation and greater tumor aggressiveness [44]. It has been shown that inhibition of IL6/STAT3 and NF κ B decreases glioma growth [45]. In the mesenchymal subgroup of GBM, poor survival is correlated with NF κ B [46]. Taken together, these studies demonstrate that controlled inflammation may prevent brain tumor initiation and progression. Anti-inflammatory medication use was associated with a protective effect against glioblastoma [47].

The Microbiome Regulates the Immune Response

The microbiome describes the totality of bacterial, fungal, and viral species in and on the body [48]. Advances in DNA sequencing technology have dramatically increased our ability to catalog microbial species [49]. In mouse models, the integration of patient exome sequencing and microbiome studies allows the identification of microbial disease markers [50]. Variations in the relative levels of gut microbial species among human individuals are the result of differences in diet, antibiotics, and general lifestyle [51]. It is believed that colonization by commensal bacteria in the neonatal gut affects the maturation of the immune system [52,53]. Gut bacteria play a fundamental role in the induction, training, regulation, and function of the host immune system [54,55]. Approximately 70% of the total immune system cells reside in the gut-associated lymphoid tissue, which comprises lymphoid and lymphocyte cells [56]. In the presence of certain commensal bacteria residing in the gut, human dendritic cells can mediate the polarization of Th cells into Th1 and Th17 to secrete proinflammatory cytokines [57].

Studies of germ-free mice demonstrate that microbiota play an important role in inflammatory responses [58]. Germ-free mice have fewer proinflammatory Th17 cells in the

lamina propria of their gut than specific pathogen-free controls [59]. Moreover, several bacterial species (e.g., lactobacilli, *Proteobacteria*, *Clostridium difficile*, enterococci, *Bacteroides fragilis*) are known to induce distinct immune cell populations that can play pro- and anti-inflammatory roles [60,61]. *B. fragilis* has been shown to drive the differentiation of IL10-secreting Tregs, which impair anticancer Th1 immunity and are involved in glioma progression and aggressiveness [62]. Furthermore, it is noteworthy that particular microbiota may lead to immune suppression [63,64]. GBM patients suffer profound local immunosuppression [6].

Gut Bacteria May Promote Tumor Development by Metabolites

Metabolites and other biologically active molecules produced in the gut may diffuse or be actively transported to the circulation and systemically affect the immune response [65]. Despite variation in the composition of the microbiome in healthy individuals, the gut microbiome's metabolic activity appears to be relatively constant. However, dramatic changes in this equilibrium may occur in response to microbiome perturbations [66]. Using mass spectrometric methods, it was shown that metabolites differ in plasma extracts from germ-free mice compared with samples from conventional animals and that these gut bacteria have a direct impact on the drug-metabolic capacity of the host [67].

In addition to CNS-related neurotransmitters and neuromodulators, the gut microbiota also produces metabolites such as short-chain fatty acids (SCFAs) that reduce the secretion of proinflammatory cytokines and induce Treg development and IL10 secretion [68]. A fraction of those circulating SCFAs may also cross into the CNS [69]. In addition, the integrity of the BBB is disrupted during neuroinflammation through the action of IL1, IL6, and TNF α [70]. It remains to be seen whether these mediators or metabolites induced by the microbiome also disrupt the BBB and induce immune suppression in the brain.

The Microbiome Has Many Routes to the Brain

The microbiota–gut–brain axis includes the brain, glands, gut, immune cells, and gastrointestinal microbiota. Mounting evidence points to the gut microbiota influencing brain function and behavior through neural, endocrine, and immune pathways [71]. CNS development is also influenced by the gut microbiota [72]. Interestingly, there has also been recent work on lymphatic vessels in the brain [73,74] suggesting a possible connection to the body's immune system and inflammation in brain cancer [75]. It has been shown that the lymphatic network links the CNS to draining lymph nodes and that its dysfunction may have a crucial role in brain cancer [76]. It is conceivable that the microbiome might exert its effect on the initiation or progression of brain tumors by impacting immune cells or metabolites that are transported to receptive precancerous areas.

The Microbiome May Impact Brain Tumor Therapeutic Interventions

The CNS is accessible by the immune system in the diseased state [18]. Moreover, GBMs attract CTLA-4-expressing T cells and express PD-L1, which inhibits the activation and continuation of the cytotoxic T cell response. PD-1 and CTLA-4 cells are able to produce

powerful coinhibitory signals in T cells. New immunotherapy strategies include monoclonal antibodies that block inhibitory T cell pathways (PD-1/PD-L1) [77]. The rationale for combining radiotherapy with checkpoint inhibitors (e.g., anti-PD-L1) in brain cancer is to enhance the immunogenicity of tumors, disrupt the BBB, and create greater antigen release [78]. It is worth noting in this context that, regrettably, radiotherapy and checkpoint inhibitors thus far have had only modest impacts on the treatment of brain tumors [79,80]. However, three Phase I trials of chimeric antigen receptor (CAR) T cells targeting IL13Ralpha2, Her2/CMV, and EGFRvIII for recurrent glioblastoma – the most aggressive primary brain tumor, with a dismal prognosis – have shown promising results [81,82]. Nevertheless, adaptive immune resistance, immune checkpoints, and other soluble immunosuppressive molecules have been identified as major obstacles [83].

Studies of the microbiome in brain cancer patients may explain the lack of success of some therapies. Recent reports demonstrate that changes in the gut microbiome weaken the outcome of chemotherapeutic cancer treatment [84,85]. In a mouse model, it has been shown that with cyclophosphamide, a conventional and widely used cancer drug, therapeutic efficacy depends on gut bacterial content. Tumor-bearing mice that were germ free or that had been treated with antibiotics showed a reduction in Th17 response, and their tumors were resistant to cyclophosphamide [84]. In another study, antibiotic-treated or germ-free mice responded poorly to immunotherapy due to lower cytokine production by the myeloid-derived tumor-infiltrating cells. Similarly, these mice did not respond well to chemotherapy due to deficient production of reactive oxygen species and cytotoxicity [85]. Finally, in germ-free mice, using specific bacteria (*B. fragilis*) it was possible to overcome the resistance to anti CTLA-4 immunotherapy [86]. In light of these results, the potential impact of the microbiome on therapeutic interventions for brain tumor should be considered.

Concluding Remarks

In this review we have summarized how inflammation and immune suppression along with the microbiome can lead to the induction and sustaining of brain tumors (Figure 1). Accordingly, we propose that certain gut microbiota in concert with the host's background may affect the body's immune system and metabolism through a gear model leading to cancer (Figure 2). These interactions (or gears), in turn, may result in altered and specifically suppressed immune function, allowing some cells to escape immune surveillance (Figure 2). Furthermore, alterations in the microbiome may also affect the metabolome, offering another gear. This interacting-gear scenario may encounter fertile ground in potential tumor cells because of somatic mutation accumulation in their genomes. Therefore, this rather permissive environment, if not outright stimulating milieu, may lead to the establishment and/or development of brain cancer and other tumors in a multistep process. Our proposed gear model (Figure 2) has direct implications for tumor etiology and, accordingly, cancer therapy. Both arms of current anticancer drug treatment (chemotherapeutic and immunomodulatory) can be enhanced through the intervention of the intestinal microbiota. Thus, in future, treatments should also target these interactions and exploit the gears whenever possible.

In conclusion, we suggest that growing evidence on a possible causal relationship between immune modulation and inflammation caused by the gut microbiome and brain cancer merit thorough consideration and investigation. The topic at hand is extremely wide ranging with many positive- and negative-feedback systems. Nevertheless, efforts to understand brain tumors from a systems-biology perspective will clarify the triggering events that interrupt the balance in this robust system leading to a dysregulated, harmful network that initiates and sustains tumorigenicity.

Deciphering the correlations between the immune system, the gut bacterial system, and brain tumor aggressiveness as well as treatment response may pave the way to a better understanding of pathogenesis, new prevention opportunities, and novel therapies for precision medicine. In addition, this strategy might open new avenues for noninvasive prediction of prognosis. Finally, more attention needs to be given to all parts of the system while treating brain tumors, including knowledge-based use of antibiotics, which fight infections but also impact the microbiome, and judicious administration of steroids, which reduce edema but also may suppress the immune system.

With new advances in tools for discovery, the next pressing question is what are the triggering events that initiate and sustain brain tumor development? Among these factors, which one links the gut bacterial system and its metabolites to inflammation, immune suppression, and brain tumorigenesis? In addition, it will be essential to discover which gut microbiota affect the success of brain tumor therapy (see Outstanding Questions). We propose that certain variants of the gut microbiome are prone to triggering inflammation and/or secreting metabolites which, in turn, may lead to immune suppression, cell proliferation, and subsequent development of brain tumors. Furthermore, response to therapy may also be affected by specific microbiota, and all will occur in conjunction with the patient's own genomic and specific variomic back-ground. Twenty-first-century precision-medicine approaches to brain tumors will include each individual's own genomic background, metabolome, particular microbiome, and immune and inflammatory state, which predispose the individual to develop brain cancer as well as impact individually tailored responses to therapy.

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Highlights

Brain tumors develop because of genetic and epigenetic factors.

Balanced immune function is important in preventing the establishment of brain tumors.

A dysregulated inflammation cascade of cytokines may sustain tumorigenicity.

The microbiome may exert its effects on tumor development by regulating the immune response, by metabolites, and by affecting response to therapy.

The success of brain cancer therapy relies on all of the factors underpinning brain cancer.

Outstanding Questions

With new advances in systems-biology discovery tools, the next pressing question is what are the triggering events that initiate and sustain brain tumor development?

What factors link the immune system, the gut bacterial system, and brain tumors?

How does the microbiome and its metabolites impact inflammation and immune suppression, which are involved in brain tumorigenesis?

Which gut microbiota affect the success of therapy for brain tumors?

Trends in Cancer

Figure 1. Proposed Pathways for How the Microbiome Affects the Brain and Brain Tumors. The microbiome in the intestinal lumen can impact the brain through metabolites as well as immune cell regulation by induction, training, maturation, or suppression followed by cytokine production. Red arrows in the right panel highlight tumor-promoting pathways, while green arrows indicate tumor-inhibitory pathways.

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Figure 2. Proposed Interlocking Gear Model Linking the Gut Microbiome to Immune Regulation and Brain Tumor Development.

Particular microbiota may exert their effects through inflammation and immune suppression along with metabolic abnormalities that, in conjunction with the accumulation of somatic mutations, may lead to brain cancer.