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INFLAMMATION AND CANCER (G-S FENG, SECTION EDITOR)

Inflammation and Gliomagenesis: Bi-Directional Communication at Early and Late Stages of Tumor Progression

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Abstract Inflammation has been closely linked to various forms of cancer. Less is known about the role of inflammation in glioma, especially at the initiation stage. In this review, we first describe the unique features of the immune system in the brain. We then discuss the current understanding of the mechanisms by which glioma cells modulate the immune system, especially how bi-directional communications between immune cells and glioma cells create an immunosuppressed microenvironment that promotes tumor survival and growth. We also address the potential tumor-initiating roles of inflammation in glioma. Finally, we describe several immunotherapy approaches currently being developed to reverse these interactions and stimulate the immune system to eliminate glioma cells.

Keywords Glioma · Inflammation · Microglia · T cell · Immunosuppression · Immunotherapy

Introduction

Inflammation is a natural immune response to an infection, tissue injury or malfunction. An acute inflammatory response begins when tissue-resident macrophages and mast cells detect an infection or damage. These cells secrete pro-inflammatory molecules that trigger a localized increase in blood flow and extravasation of plasma proteins and leukocytes to the affected tissue, leading to the typical swelling and redness. Once the immune response has neutralized the threat, pro-inflammatory molecules are replaced with anti-inflammatory molecules and the inflammation subsides. However, if the cause(s) of the initial inflammatory response are not resolved, an acute inflammation can transition to a chronic inflammation, lasting weeks, months, or even years. Whereas acute inflammation is beneficial, helping to eliminate infectious agents and promote tissue repair, chronic inflammation can have deleterious effects, such as tissue damage, autoimmune disease, or even cancer growth.

While immune surveillance blocks tumor formation, inflammation is known to promote tumorigenesis in many circumstances [1–4]. For example, cancer can be caused by inflammation triggered by infections (Hepatitis B/C-associated hepatocellular carcinoma, *H. pylori*-associated gastric cancer), autoimmune diseases (colitis-associated colorectal cancer) and even environmental irritants (asbestos-associated mesothelioma). Inflammation can promote tumorigenesis via increased genetic alterations, resulting from macrophage-secreted reactive oxygen and nitrogen species or activation-induced cytidine deaminase, a mutagenic enzyme. In the gut, inflammation strips away protective mucosal layers, exposing stem cells to environmental carcinogens and releasing them from normal homeostatic controls. Additionally, some cytokines secreted during the inflammatory response promote tumor growth by inducing angiogenesis, or by triggering signaling cascades that activate NFκB and STAT3, which in turn activate proliferative and anti-apoptotic genes [5, 6]. Three interesting themes emerge from these studies. First, inflammation can either inhibit or promote tumor growth, depending on the combination of immune cells present and the signaling factors they

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secrete. Second, the impact of inflammation on mutant cells could evolve as tumors progress from benign to malignant stages. Third, the interactions between immune and tumor cells are bi-directional, which adds another layer of complexity to this problem.

The role of inflammation in glioma is less clear than in the aforementioned cancer types. Gliomas are a form of cancer in the central nervous system (CNS) with diverse pathological and histological properties. The most common form, glioblastoma multiforme (GBM), is one of the deadliest of all cancers and has a median survival period of 12–14 months. Epidemiological studies have suggested a link between inflammation and glioma. Understanding how the immune system and gliomas interact could lead to novel therapeutic approaches to combat glioma. In this review, we will discuss the unique features of immunity in the CNS, the potential roles of inflammation in causing gliomagenesis, the known effects of inflammation in malignant gliomas, and how we could take advantage of the interactions between immune and tumor cells to more effectively treat glioma patients.

CNS Immune System

The brain is commonly known as an immune-privileged organ due to the restrictive nature of the blood–brain barrier (BBB) that prevents immune cells and serum-derived immune modulators from accessing it [7]. In the absence of pathological damage, the only cells with immune functions in the CNS parenchyma are microglia. However, immune cells from the hematopoietic system play important roles in the brain when the BBB is compromised by physical trauma or pathological conditions including multiple sclerosis, stroke, and malignant brain tumors.

Microglia

Microglia share a common origin with the hematopoietic system but segregate into a unique lineage early in development. They are generated from primitive myeloid progenitors in the extra-embryonic yolk sac before E8 [8]. After entering the CNS at E10 [8•, 9], microglia appear to replenish themselves solely through self-renewal without the involvement of peripheral macrophages, their bone marrow-derived close relatives.

In a healthy CNS, branched (resting) microglia actively monitor their environment by constantly extending/retracting their processes, while maintaining a static cell body [10, 11]. A resting microglia is activated when it detects pathogen-associated molecular patterns (PAMPs; ex. LPS) or damage-associated molecular patterns (DAMPs; ex. extracellular matrix molecule fragments) through their binding to pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD) proteins, and c-type lectin receptors. Serum proteins and dysfunctional neurons can also trigger microglial activation (see below). Activated microglia become amoeboid and can exist in different states representing different outcomes of the immune response. Similarly to macrophages, microglia can be classified under M1 (classic activation) and M2 (includes alternative activation and acquired deactivation) activation states [12•]. Classically activated microglia upregulate the expression of MHCII, thus increasing their antigen-presenting ability to activate T cells, secrete pro-inflammatory cytokines including TNFα, IL6 and IL1β, and upregulate nitric oxide synthase (NOS) to produce NO to destroy pathogens. Macrophage transition from classic to alternative activation is regulated by T cell-derived IL4 and IL13. Although their source in the CNS is unclear, IL4 and IL13 can also shift microglia-mediated immune responses, from pro-inflammatory and destructive to anti-inflammatory and tissue regenerating, by downregulating TNFα, IL1β and NOS2 and upregulating arginase 1, mannose receptor, FIZZ1, and Ym1 [13, 14]. However, it is currently challenging to determine whether these effects are truly microglia-specific or if they were observed in macrophages infiltrating the CNS [12, 15]. Acquired deactivation also shifts microglial responses to an immunosuppressive state, but is mediated by TGFβ and/or IL10. Additionally, acquired deactivation is characterized by microglial phagocytosis of apoptotic cells, which also acts as a signal to "deactivate" microglia [12].

Infiltrating Immune Cells Upon BBB Breakdown

Activated microglia secrete pro-inflammatory cytokines such as IL1β, which modulate the BBB to allow bone marrow-derived immune cells into the CNS [16], including $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells. The latter are subdivided into Th1, Th2, and Th3, which have different effects on an immune response [17]. Th1 cells promote a pro-inflammatory state by secreting cytokines such as IFNγ and IL12, activating macrophages and microglia to release toxic compounds such as NO, and activating cytotoxic $CD8^+$ T cells. On the other hand, Th2 cells secrete anti-inflammatory cytokines such as IL4, IL10, and IL13, which counteract the effects of Th1 cells and promote B lymphocyte activation and antibody production. The main role of Th3 cells is to suppress the immune response by secreting TGFβ. However, Th1 cells can also produce anti-inflammatory cytokines, such as IL10 and TGFβ, later in an immune response to limit the length of the cytotoxic, tissue-damaging phase of this response. Another important type of $CD4^+$ T cell is the regulatory T cell (Treg), which has mainly anti-inflammatory, immunosuppressive roles due to the production of high levels of IL10 and TGFβ as well as other, unknown

mechanisms. These cells play an important role in shutting down an immune response once the threat to the host has been eliminated as well as in prevention of autoimmune disease [18].

Macrophages also enter the CNS upon BBB breakdown. However, due to similar marker expression and functions to microglia, and other experimental caveats, it has been very difficult to study the distinct contributions of infiltrated macrophages versus resident microglia to CNS immune activities [19], particularly in pathological cases. Nonetheless, significant differences have been identified between these cell types. Compared to macrophages, microglia have attenuated immune properties, such as poor antigen-presenting ability (reduced MHCII levels) and reduced phagocytic ability. Additionally, the BBB shields microglia from serum proteins including fibrinogen, a strong activator for both macrophages and microglia [20]. Lastly, healthy neurons signal to microglia through a variety of receptor/ligand complexes that keep them in a resting state [21]. Overall, the unique properties of microglia in the CNS are likely critical to avoid excessive damage in an organ with limited regenerative ability.

The Impact of Astrocytes on CNS Immunity

Though not part of the immune system, astrocytes also play a significant role in modulating immune responses in the CNS [22]. Astrocyte end-feet form the *Glia limitans*, the last barrier to immune cell entry into the CNS [23]. Upon trauma or in autoimmune diseases, reactive astrocytes form a barrier to the infiltration of the CNS by peripheral leukocytes [24]. Similar to microglia, astrocytes express various PRR receptors, such as TLR3, and are thus capable of responding to pathogens and tissue damage. Once activated, reactive astrocytes can secrete pro-inflammatory cytokines and chemokines that can activate and recruit immune cells to the affected CNS region (IL6, CCL2, and others). Finally, reactive astrocytes can secrete trophic factors such as CNTF and IGF1 that participate in the tissue repair phase of inflammation [22]. It has also been suggested that astrocytes can act as antigen-presenting cells (APCs), thus directly participating in T cell activation, though this remains a controversial issue [25].

Inflammation in Glioma

To understand the role of inflammation in gliomagenesis, we will discuss both the initiation and the malignant stages since inflammatory cells and molecules are involved in both stages, though in different ways. We will also discuss the complex nature of this topic, especially the anti- and pro-tumor activities of inflammation and the two-way interactions between immune and tumor cells.

Can Inflammation Cause Glioma?

Epidemiological studies suggest a link between inflammation and gliomagenesis: individuals with a history of NSAID use, asthma, allergies, or high IgE levels have decreased risk of developing glioma, whereas use of antihistamines (lowers IgE levels, used to treat allergies and asthma) has the opposite association [26–29]. It has been hypothesized that allergic reactions and high IgE serum levels might lead to lower levels of Tregs, a cell type known to cause chronic, tumor-promoting inflammation [30]. Additionally, a number of studies have revealed associations between SNPs on immune-related genes and risk of glioma [30, 31], including the anti-inflammatory IL4, IL4R, IL10, and IL13, and the pro-inflammatory Cox2 and IL6. However, functional studies will be needed to verify such associations. It is interesting to speculate that, similar to how inflammatory bowel disease can cause colorectal cancer, autoimmune diseases affecting the CNS might also contribute to gliomagenesis. In fact, some multiple sclerosis patients develop glioma in the lesioned areas years later [32, 33]. A similar link has been suspected for head trauma [34, 35]. However, these associations are not highly significant due to the relatively low number of cases.

One intriguing possibility for how inflammation might influence gliomagenesis is by affecting the behavior of glioma cells of origin. Recent studies have identified both neural stem cells (NSCs) and oligodendrocyte precursors (OPCs) as cell types that, when mutated, can give rise to malignant gliomas [36•• , 37••, 38••]. Interestingly, molecules produced during inflammation can affect the behavior of both cell types (Fig. 1). Activated microglia and astrocytes secrete MCP1/CCL2 and SDF1 that can promote NSC migration to the inflamed area [39–42]. Pro-inflammatory cytokines can also recruit OPCs to promote repair of demyelinated lesions, and TNFα in particular can promote OPC and NSC proliferation [43–45]. Additionally, alternatively-activated microglia upregulate arginase 1, leading to the production of polyamines, which can promote NSC proliferation [46]. Conversely, TGFβ, which can be secreted by microglia, has well-known anti-proliferative effects on many types of CNS progenitors [47]. However, these effects are highly context-dependent, as microglia in the classic or alternative activation states can respectively inhibit or promote neurogenesis [48]. Similarly, high or low levels of IFNγ can inhibit or promote neurogenesis [49–51], and TNFα signaling through TNFR-I receptor inhibits hippocampal progenitor proliferation, whereas signaling through TNFR-II has the opposite effect, particularly in pathological

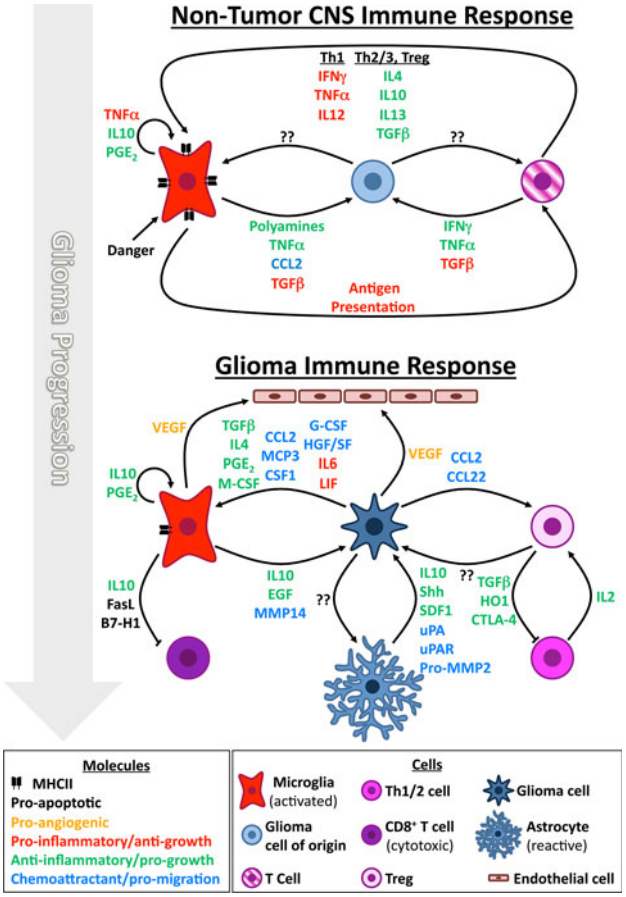

Fig. 1 Effects of inflammation on glioma initiation and growth. While the depicted cellular interactions are known to occur, a link between inflammation and glioma progression has only been suspected. Inflammatory molecules can affect immune cells (pro- or anti-inflammatory) and glioma cells of origin/glioma cells (anti- or pro-growth). Some inflammatory molecules can be pro- or anti-growth depending on the circumstances (see text for details; not all cells or interactions were represented)

conditions [52]. The study of interactions between neuroglial progenitors and immune cells is in its infancy, but has the potential to deliver critical insights into the effect of inflammation on glioma initiation.

Inflammation in the Malignant Phase: Friend or Foe?

The inflammatory response to a glioma is complex, with multiple cell types involved in multi-lateral communications (Fig. 1). Because gliomas cause a breakdown of the BBB, circulating immune cells not normally found in the CNS now gain access to tumor areas. This includes various types of T cells, B cells, macrophages, and myeloid-derived suppressor cells (MDSCs). Additionally, astrocytes become reactive and also participate in the response to the tumor. Finally, the tumor cells themselves secrete a number of factors that modulate the activity of all the cells mentioned above (as well as endothelial cells).

It has been estimated that up to 30 % of the glioma mass is composed of microglia [53]. Though these estimates can vary [54], the importance of microglia to the glioma microenvironment is unquestionable. Tumor-derived chemokines (MCP1/CCL2, MCP3, CSF1, G-CSF, HGF/SF) [55–61] attract microglia to gliomas, where they become activated. However, rather than engaging in cytotoxic or phagocytic activities, glioma-associated microglia tend to secrete cytokines and growth factors that promote tumor cell growth and angiogenesis, such as IL10 [62, 63], EGF [64], and VEGF [65]. Microglia-derived IL10 can also inhibit T cell proliferation and confer an immunosuppressed state. Glioma-associated microglia express MHCII and B7 molecules at the cell surface [66, 67]. This would allow microglia to act as APCs and activate a cytotoxic T cell response (via Th1 activation). However, glioma-associated microglia appear to have low APC activity [68], as they express lower levels of MHCII molecules than microglia activated in the absence of tumor cells [66, 67, 69] and lack expression of co-stimulatory molecules CD86, CD80, and CD40 [54]. Data suggest that this inhibition of microglial antigen-presenting capability is at least partially due to glioma-derived IL10 and prostaglandins [70]. In fact, many cytokines secreted by glioma cells can directly inhibit MHCII production in microglia [71]. Furthermore, glioma-associated microglia can actively eliminate T cells via FasL- and B7-H1-mediated apoptosis of $CD8^+$ T cells [72, 73]. Decreased antigen presentation and T cell apoptosis are normal microglial negative feedback mechanisms to avoid destructive inflammation in the CNS, which are apparently hijacked by glioma cells to avoid elimination by the immune system.

In fact, the glioma microenvironment is strongly immunosuppressive, reminiscent of the M2 phase of inflammatory responses. Hao and colleagues [74] characterized the expression of 53 cytokines and receptors in multiple human tumors and found that the Th2/3 (immunosuppressive) profile was dominant over the Th1 (pro-inflammatory) profile. Consistent with this finding, TLR stimulation in glioma-associated microglia does not trigger classic activation, since these cells fail to secrete pro-inflammatory cytokines (IL6, IL1β, TNFα) and are thus incapable of activating a cytotoxic state in $CD8^+$ T cells [54]. This immunosuppressive state is due to multiple factors secreted by glioma cells themselves. Glioma-derived M-CSF can drive glioma-associated microglia towards an M2 phenotype [75]. Other factors also increase prostaglandin-E_2 (PGE_2) production by microglia, which then has an autocrine effect decreasing microglial production of TNFα [76]. Glioma cells are known to express IL4 and PGE_2 [77••], both of which can induce microglial alternative activation (see above). Similarly, TGFβ, a strong inducer of acquired deactivation [12], is also expressed by glioma cells [78, 79]. TGFβ plays a number of roles in the glioma microenvironment, including

suppression of pro-inflammatory responses from T cells and microglia, but can also act directly on glioma cells to promote their growth. Several reports indicate that a subpopulation of glioma cells with tumor-initiating ability (cancer stem cells) are direct targets for TGFβ pro-tumorigenic effects [80–82]. Interestingly, TGFβ signaling has opposite effects in the pre-malignant and malignant phases of cancer for reasons that are just beginning to become apparent [47, 83]. In addition to anti-inflammatory cytokines, glioma cells also secrete IL6 and LIF [74, 84, 85], which could stimulate microglial classic activation or act on the glioma cells themselves to promote proliferation [86], and pro-angiogenic VEGF [65, 87], giving the tumor access to nutrients and oxygen. The glioma immunosuppressive environment is further enhanced by elevated numbers of Treg [54, 88]. These cells are recruited by glioma-derived chemoattractants (CCL2, CCL22) and can suppress T cell proliferation and promote an anti-inflammatory profile [89, 90]. The mechanisms by which Tregs exert these effects are still unclear, but it appears that expression of heme oxygenase 1 (HO1) plays an important role, perhaps via the production of carbon monoxide [91, 92]. Other mechanisms involve CTLA-4 and TGFβ [93]. Importantly, depletion of Tregs in mouse glioma models improves survival [94].

There are indications that, just as in other forms of cancer where inflammation plays a pro-tumorigenic role, STAT3 and NFκB, key nodes of cytokine intracellular signaling, are central to this effect. STAT3 inactivation changes the profile of glioma-associated microglia from anti- to pro-inflammatory and decreases glioma growth [95–97]; NFκB activity seems to block glioma cell differentiation while its inhibition promotes glioma cell senescence [98], whereas deletion of NFKBIA, an NFκB inhibitor, is associated with more aggressive gliomas [99].

In addition to immune cells, reactive astrocytes are also commonly found within gliomas. These cells secrete Shh [100–102], SDF1 [103–105], and IL-10 [62], which support glioma cell survival and proliferation. Astrocytes also play important roles for the enhancement of glioma cell migration, a property of gliomas that makes them particularly difficult to cure. UPA/uPAR from astrocytes cleaves plasminogen secreted by the glioma cells to plasmin, which in turn cleaves astrocyte-secreted pro-MMP2 to MMP2, thus increasing glioma cell invasiveness [106]. Additionally, glioma-secreted factors stimulate microglia to release MT1-MMP (MMP14) which can then activate glioma-derived pro-MMP2 [107]. Other molecular interactions and cellular players in the glioma microenvironment are not covered in this review due to space constraint, but we refer interested readers to recent reviews for more details [77••, 108••].

In summary, while the immune system can detect the presence of a glioma in the CNS and responds with mobilization/activation of many cell types, this response appears to be subverted from a pro-inflammatory, classic activation state to an immunosuppressed, alternative activation state by glioma-derived factors. If this tolerant, subverted state can be changed back to a pro-inflammatory state, then the immune system could help eliminate the glioma cells. Multiple efforts are currently underway to devise therapeutic strategies based on that concept.

Glioma Immunotherapy

The concept of cancer immunotherapy has existed for many years. It is based on recruiting the patient's immune system and enhancing its anti-cancer properties to help eliminate the tumor cells [109•]. Passive immunotherapies use immune effector molecules (antibodies and cytokines) to elicit a rapid, but short-term, anti-tumor response. Active immunotherapies enhance T cell anti-tumor activity (autologous grafting of APCs exposed to tumor peptides or direct peptide injection) and can therefore confer a longer-lasting protection against cancer. Comprehensive reviews of the current state of glioma immunotherapy can be found in recent publications [110••, 111••]. Below, we discuss examples of promising glioma immunotherapies as well as approaches that have shown promise in other types of cancer and might soon be used against glioma.

One of the prerequisites of immunotherapy is the existence of antigens specific to glioma cells, a rare occurrence since tumors are composed of "self" cells. One candidate is EGFRvIII mutant receptor, which is not expressed by normal cells and has a prevalence of 20–30 % in GBM patients [112]. Immunization against EGFRvIII-specific antigens has shown safety and increased survival in glioma mouse models and patients [113, 114]. Unfortunately, immunotherapies based on EGFRvIII epitope alone eventually recur from tumor cells that had no EGFRvIII expression [114], illustrating the need for immunization against multiple tumor epitopes by using inactivated whole tumor cells as the immunogen [115–119]. Recently, several groups have reported high levels of cytomegalovirus (CMV) in human gliomas [120, 121], sparking interest in using "non-self" CMV antigens to mount an anti-glioma immune response [118].

In addition to unique antigens, immunotherapy can only be effective after overcoming the immunosuppressive environment created by gliomas. Some attempts have focused on inactivation of Tregs: CD25-blocking antibodies (IL2Rα, central to Treg function) have been used with some success in mice and humans [94, 122–124], and TLR8 and TLR9 stimulation can reduce Treg accumulation in glioma and improve $CD8^+$ T cell activity [125, 126]. Other approaches could be to inhibit the CCL2/CCL22 chemokine receptor CCR4 to prevent Tregs from being attracted to the glioma site [89, 90].

Recent successes in immunotherapy for other cancers have re-ignited interest in this field [109]. Activity-blocking

CTLA-4 antibodies are showing promise in the treatment of metastatic melanoma. This approach could also prove effective against glioma, where CTLA-4 plays a role in Treg-mediated immunosuppression. CTLA-4 also plays a direct role in downregulating effector T cell activity, and thus inhibiting it in gliomas could also improve these cells' function in the tumor, provided there are cells with antigen-presenting ability to stimulate them. Another attractive candidate target for immunotherapy is PD-1, the receptor for PD-L1 (B7-H1), which can reduce proliferation and induce apoptosis of $CD8^+$ T cells. PD-1-inactivating antibodies have been tested with encouraging results in phase I clinical trials for metastatic melanoma, colorectal cancer, non-small cell lung cancer, prostate cancer, and renal cell carcinoma [127]. As the mechanisms mediated by PD-1 and its ligand are known to occur in glioma (see above), this approach could also one day be beneficial for glioma patients.

Conclusion

Just as many parasites have developed strategies to evade immune rejection [128–130], gliomas seem to use similar approaches to avoid elimination by the immune system. By secreting immune-modulating factors, glioma cells convert microglial and macrophage activation away from a pro-inflammatory, classic state towards an anti-inflammatory, alternative activation state. This permissive environment is further enhanced by attracting Treg and other immunosuppressive cells into the tumor mass. Such modulations not only passively allow tumor cells to survive but can also promote their growth, possibly by engaging immune cells into a tissue repair mode. Therefore, rigorous studies are urgently needed to uncover the two-way communications between glioma and immune cells. Importantly, to fully understand the impact of inflammation on gliomagenesis, we should study such relationships not only in malignant gliomas but also during tumor-initiation stages, where many important questions remain to be answered. Do pre-malignant mutant cells trigger microglial activation, and if yes, then by which mechanism? If no, how do they evade detection? Do microglia initially try to eliminate mutant cells, or can mutant cells subvert microglial responses from the earliest stages towards a growth/survival-promoting role? Do these interactions accelerate gliomagenesis? Genetic mouse models of glioma can be particularly helpful in answering these questions due to the ability to follow mutant cells throughout their malignant progression in a physiologically relevant environment. Ultimately, therapeutic strategies that can thwart the subversive tricks of tumor cells and turn the immune system against them will yield tremendous clinical benefits. The challenges are great, but collaborations between immunologists, neuroscientists, and oncologists should make a cure possible.

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- •• Of major importance

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