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Immune Connection in Glioma: Fiction, Fact and Option

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1. Introduction

After the hypothesis of 'immune surveillance' in tumor proposed in 1970, several investigations showed the evidences of its existence where immune system is able to recognize the defects due to tumor onset (MacFarlan Burnet, 1970). But how far this surveillance is effective in the compartmentalized brain in case of glioma still remains a big uncertainty. Glioma is one of the deadliest types of cancer for its rapid growth, invasiveness and short life expectancy of the victim. So, figuring out of the extent of host immune efficiency in glioma is crucial. As glioma is able to create a hostile environment for the immune cells by releasing different soluble factors, expressing death receptors and by receptor camouflaging etc, the working situation for the host immunity becomes more difficult. Therefore, proper assessment of the role of brain immune connection in glioma is crucial to explore the probable level of support that can be extended by the immune defense mechanism against glioma. This immune resistance is also vital to support the present therapeutic modalities including adjuvants used for treating glioma.

2. Death of 'Privilege' myth: Immunocytes do not spare brain from their vigilance

2.1 'Immune privilege' of brain: A notion that prevailed more than 5 decades

At the beginning of 20th Century, brain was thought to be a separate organ mostly abandoned by the immune system. The initial evidences of immune compromise of the brain compartment were observed from 1920s with the tumor tissue transplantation studies. Rat sarcoma, when transplanted in mouse brain parenchyma, was found to grow better in comparison to its subcutaneous and intramuscular (systemic) transplantations (Shirai, 1921). On contrary, when portions of recipient spleen were co-transferred with tumor in brain parenchyma, inhibition in tumor growth occurred (Murphy and Sturm, 1923). Thus a weak or less efficient immune intervention in brain was conceptualized and the term 'immune privilege' was proposed by Billingham and Boswell (Billingham & Boswell, 1953).

With this, another set of observations in late 19th century and afterwards developed a concept of existence of a barrier between blood and CNS tissue. Basically, Paul Ehrlich's observation with the intravenous administration of vital dye in experimental animals

showed infiltration of the dye in other organs except brain. That led him to propose a barrier between brain and blood stream (Ehrlich, 1885 & 1904). Goldmann's study showed that tracers injected in blood do not enter into the parenchyma proper in brain, but accumulated in the choroid plexus, perivascular space or lymphatic clefts (Obersteiner, 1870; Goldmann, 1913). The 'no entry' status of blood immunocytes was further fueled with the xeno- and allogenic tissue transplantation studies (Medawar, 1948; Barker & Billingham, 1977). In the following decades ultrastructural studies of the blood capillaries in brain showed the distinct cellular organization present in the interphase of blood and brain that prevent the flow of blood immunocytes and large molecular weight solvents into brain (Reese & Karnovsky, 1967; Engelhardt & Wolburg, 2002). Thus blood-brain-barrier (BBB) encapsulates the brain and seems to maintain the 'immune privilege' status. Till 1980s no direct lymphatic drainage from nervous system was detected. Negligible expression of MHC and undetected dendritic cells (DC) in brain indicated the inefficiency of antigen presentation in the organ (Sedgwick, 1995; Perry, 1998).

2.2 Detection of secret routes connecting brain with systemic circulation

But in last two decades a paradigm shift has occurred in this 'immune privilege' rank of brain. Basically, three obstacles that maintain the privilege are – i) lack of drainage of CNS antigens at least to cervical lymph node, ii) hindrance to easy access of T cells in the CNS parenchyma and iii) T cells require antigen presentation in the reaction site by the APCs which were thought to be scarce in brain. Initial experiments suggested that CNS antigens can drip outside passively by a different route along the olfactory nerves on to the cribriform plate which is connected to the lymphatics of nasal submucosa and finally to the cervical lymph node (Cserr & Knopf, 1992; Sedgwick, 1995). Tracer studies indicated CSF drainage to cervical lymph node (Boulton *et al*, 1999). CSF circulates from ventricles through subarachnoid spaces (a space between arachnoid and pial membrane filled with CSF and surround the brain and spinal cord) and it has access to Virchow-Robin space that surrounds blood vessels when they enter brain parenchyma [Figure – 1]. Ependymal lining of the ventricles lack 'tight junctions' and in other specialized perivascular spaces including Virchow-Robin's that porosity is also present, which help in clearance of interstitial fluid from brain parenchyma (Ransohoff *et al*, 2003; Piccio *et al*, 2002). So the protein antigens have the probable, though slightly difficult than other organs, access to the lymphoid tissue through CSF. This generates opportunity for the passage of immunocytes.

The afferent arm of CNS immune response is initiated with the antigen leakage from brain parenchyma to CSF; whereas the efferent arm is largely progressed with the migration of leukocytes to CNS into different routes. Ransohoff and colleagues identified three distinct routes which are – i) cells from blood extravasate through choroid plexus to the CSF, ii) leukocytes flowing through internal carotid artery cross the post capillary venules in the subarachnoid space and Virchow-Robin perivascular space and iii) finally leukocytes may cross the BBB deep into the brain to enter directly into the brain parenchyma (Ransohoff *et al*, 2003). Precisely speaking, BBB is a metaphor that describes the property of brain vasculatures restricting the entry of large molecules and cells (Bechmann *et al*, 2007). The perivascular spaces exist in the pre- and post-capillary segments in brain where a heterogeneous assembly of lymphocytic and monocytic cells are observed, more during inflammation. Both in the perivascular spaces and after entering into parenchyma they encounter antigen presenting cells (APCs) to continue the immune response in brain.

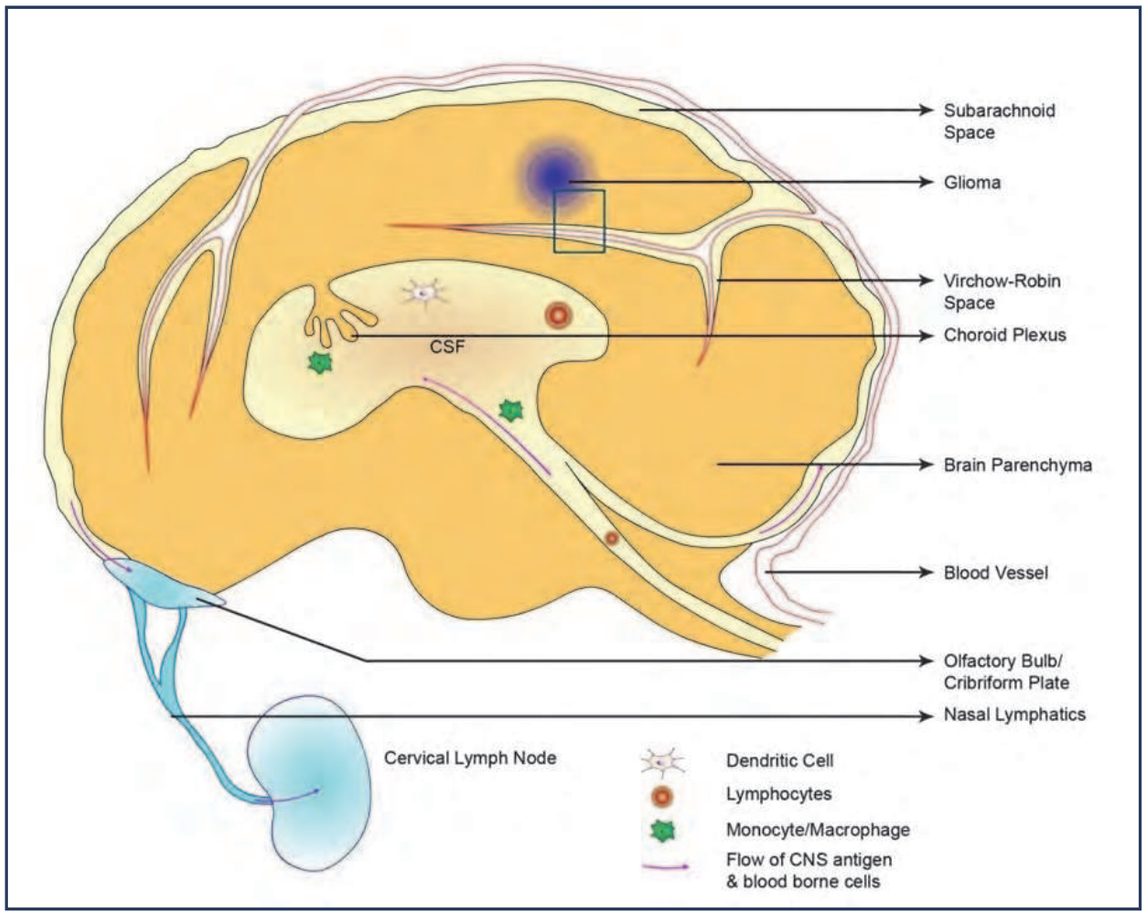

Fig. 1. This figure represents routes of CNS antigen escape and immune cell connection from brain to peripheral circulation. T cells initially are primed by the CNS antigen leaked from brain to the cervical lymph node or olfactory bulb or nasal mucosa, become activated and reach to the blood vessel, subarachnoid area, Virchow-Robin space or perivascular space and CSF in brain. There also a repriming of the glioma antigen specific lymphocytes occurs by the APC circulating or residing at those spaces. Choroid plexus is also a very important route of this CNS antigen escape and site of antigen presentation to lymphocytes by the local APCs. These specific glioma antigen primed activated lymphocytes enter into the brain parenchyma and invade towards glioma. [The box has been elaborated in Figure – 4]

2.3 Lymphocytes assess CNS antigen and enter into neuropil

2.3.1 T cells can pass into neuropil and interact with brain APCs

Early experiments showed that though graft rejection is comparatively slow in brain, once the graft is familiar to the immune system outside brain, the rejection occurs rapidly (Mason *et al*, 1986; Sedgwick, 1995). Simultaneously, Wekerle and colleagues demonstrated that activated or antigen primed T cell from the periphery can cross the BBB nonspecifically (Wekerle *et al*, 1986). Following experiments supported the fact when it was found that CD4+ T cell blasts of any specificity injected intravenous to experimental animals can pass into CNS tissue, although myelin antigen specific T cells are found to remain longer (Hickey *et al*, 1991). This delay of the myelin antigen specific T cells suggests some mechanism that

holds them to process and react in brain parenchyma. The answer is the cross-talk between them and microglia (or brain APC). Microglia is found *ex-vivo* to induce IFN-γ and TNF production from CD4 T cells as their effector activation, but do not support proliferation by IL-2 and induce apoptosis. Interestingly, perivascular macrophages show activation with IL-2 mediated proliferation and survival of CD4+ T cells (Ford *et al*, 1996).

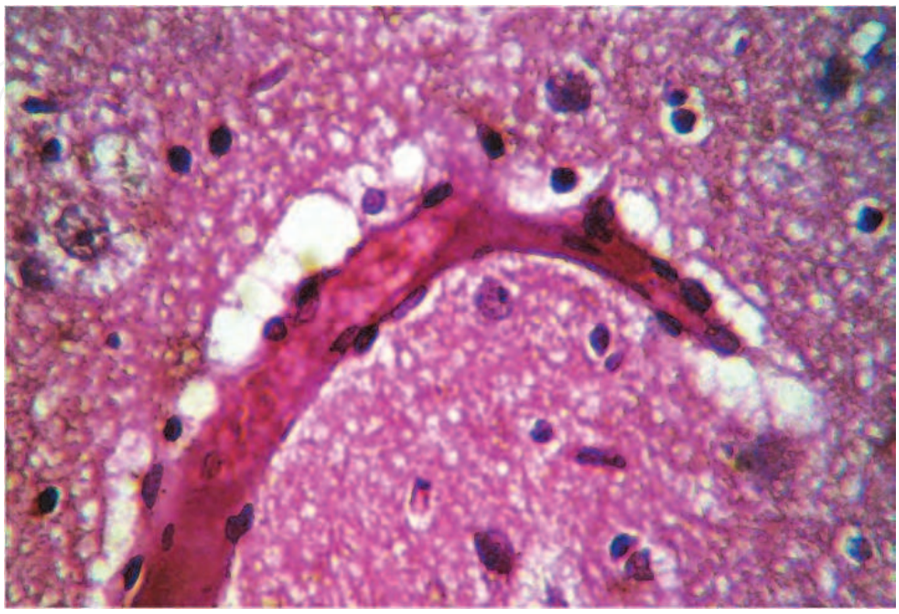

Fig. 2. This section of brain parenchyma shows a blood capillary containing leukocytes. Many of them are at the margin of the capillary, tethering the endothelium and extravaseting at the perivascular spaces. Perivascular microglia/macrophage are visible. Few infiltrated leukocytes are found scattered in brain parenchyma. At least one rod shaped ramified microglia is detectable in the parenchyma. A simple H/E staining section of brain furnishes these visual evidences of neuro-immune connection. (Magnification 1000X, oil immersion in Olympus CH20*i* Microscope and photographed by Olympus DSC)

The reverse is also visible in the GvHD affected CNS model where $CD4^{+}\alpha\beta TCR^{+}CD2^{+}$T cells infiltrat and scatter deep into neuropil or brain parenchyma. The microglial cells show activation with many fold increase in their CD11b/c, CD45 and MHC class II expression and cluster with intimate association with these T cells *in situ* that lead to microglial activation, proliferation and expansion (Sedgwick *et al*, 1998). Thus both microglia and infiltrated lymphocytes influence each other for their maturation and effector function in brain.

With the citations of entry of lymphocytes in brain, the role of CNS APCs started to come into surface. They are subdivided as microglia and perivascular macrophages based on their position, morphology, immunophenotype and functional priority (Sedgwick *et al*, 1991; Bechmann *et al*, 2001). Therefore entry of lymphocytes into neuropil through pre- and post-capillary vessels needs a two step process. Crossing the vessel endothelium, muscle layers and basement membranes lymphocytes and blood borne monocytes reside at the perivascular space encapsulated with glial limitans and pericytes. Next step is more restricted where the leukocytes cross the layer of glial limitans and step in to neuropil (Bechmann *et al*, 2007). To proceed for this step, brain APC associated with this limiting

layer is crucial (Tran *et al*, 1998; Greter *et al*, 2005) [Figure – 2]. Then the infiltrated lymphocytes may come across the APC present in the brain parenchyma or at the site of pathogenesis. The T cell-microglia interactions in CNS autoimmune encephalomyelitis (EAE) or brain tumor; T cell secretion of Th1 cytokines to mature microglia as functional APC and resulting restimulation of leukocytes by them; counter regulation of this inflammation by Th2 induction by microglia etc had been detailed mostly on the functional studies committed so far (Aloisi *et al*, 2000; Ghosh & Chaudhuri, 2010).

2.3.2 Cell tracking experiments visualize leukocyte access in brain

But a new generation of cell tracking experiments and lebelling methods now provide us more direct evidences of the events occurring beneath the skull. GFP-labelled unspecifically activated CD4 T lymphocytes when injected into cortex and ventricle of mice brain, there path through the cross-section of entire head-neck region was monitored. Irrespective of the sites, it was visualized that they pass through the cribroid plate, reach to nasal mucosa and accumulate in the cervical lymph node (Goldmann *et al*, 2006). Shifting the focus on CD8+ T cells, it was recently found that selective traffic of antigen specific CD8 T cells occurs in brain. Using immunofluroscence and confocal micrographs it was found that the process is dependent on luminal expression of MHC class I by cerebral endothelium in response to intracerebral antigen injection. Significantly, the process is quite independent of perivascular macrophages and different from CD4+ T cell entry (Galea *et al*, 2007). After visualizing the entry and exit of T cells from brain their activities in the brain needs a close watching.

3. But glioma makes the immune system puzzled

Despite the efforts of host immune system, which Burnet and Thomas described as 'immune surveillance', malignant glioma can evade and overcome this defense to grow. There are several generalized strategies for the tumor cells to bypass the immune resistance. They can be simply categorized as follows –

a. Making the immune system ignorant about the tumor growth by lacking the tumor antigens in lymphoid organs, growing in immune privileged position, creating physical barriers by stoma, lacking adhesion molecules for cellular interactions etc.
b. Actively impairing and suppressing the immune system by down-regulating the expression of MHC genes or imposing defects in antigen processing, secreting suppressive cytokines like TGF-β, IL-10 etc and other factors like prostaglandins.
c. Inducing tolerance to immune system by minimizing costimulation that results into anergy and central tolerance to the tumor antigen as many of them produce self-antigens or mimic them. Regulatory T cell mediated inhibition of DC maturation and T cell activation in the tumor environment plays a crucial role for dampening the immune resistance.
d. Counter attacking the immune system by expressing different death receptor ligands like CD95L, decoy receptors, TRAIL family etc and expressing anti-apoptotic molecules for themselves.

Glioma adapt most of these mechanisms successfully with their additional advantage to grow in a position which has been visited or monitored by the peripheral immune cells less frequently and less aggressively.

3.1 Glioma drastically reduces immune efficiency

Different studies on a number of patients harboring glioma revealed that they suffered from impaired cell mediated immunity (Elliott *et al*, 1984). *In vitro* studies showed that peripheral blood lymphocytes (PBL) obtained from patients with gliomas proliferated poorly in response to mitogen and/or antigen stimulation *in vitro* and unresponsiveness to T-cell mitogens concanavalin A (ConA), phytohemagglutinin (PHA) and anti-CD3 mAb etc (McVicar *et al*, 1992). A number of potential mechanisms explaining the observed immune-suppression including qualitative or quantitative alterations in cell surface marker expression on T-cells, elevated suppressor cell activity or T-cell lymphopenia were explored. T-cells obtained from glioma patients have intrinsic defects, which synthesize and secrete less than normal levels of interleuken-2 (IL-2) required for T-cell proliferation. IL-2 mRNA synthesis is impaired with less production of IL-2 receptor (IL-2R), and they also are unable to enter G1 phase of cell cycle (Elliott *et al*, 1990). Additionally, the numbers of $CD4^+$ T-cells obtained from patients are reduced to a great extent than $CD8^+$ T-cells, which predominately infiltrate glioma, but are deprived from $CD4^+$ help. Based on their inability to produce and respond to IL-2 and lack of $CD4^+$ help, T-cells obtained from glioma patients appear to be anergic (Elliott *et al*, 1990; Giometto *et al*, 1996).

Wide level of T-cell signaling defects are observed in glioma patient derived T-cells. T-cells from glioma patients show reduced tyrosine phosphorylation compared to normal T cells, which is mostly reduced in PLCγ1. Additionally, both PLCγ1 and $p56^{lck}$ protein levels are found reduced dramatically and thus it causes the overall impairment of TCR/CD3-mediated signaling. Reduced $p56^{lck}$ and associated signals also resists the cells to make sufficient contact with APCs, reduced their appropriate stimuli and movements (Marford *et al*, 1997, Dix *et al*, 1999). Severe T-cells lymphopenia i.e. rapid depletion of the cells is an important feature of glioma patients. As $CD4^+$ T-cells are reduced in number and less responsive to mitogens and antigens, IL-2 and IFNγ production decreases further. Because both these cytokines are important for generation of LAK cells and CTL activity, they are responsible for impaired generation of antigen-stimulated, MHC-unrestricted cytotoxicity observed in glioma patients (Urbani *et al*, 1996; Dix *et al*, 1999). Even glioma condition facilitates to increase Th2 type IL-10 production and inhibit Th1 type IL-12 and TIL secrete predominantly Th2 type cytokines underscoring the Th1 effect. Glioma has been shown to synthesize and secrete multiple factors including TGFβ, PGE_2, IL-10 and gangliosides (Zou *et al*, 1999, Huettner *et al*, 1997). Gliomas synthesize and secrete $TGF\beta_{1,\ 2,\ and\ 3}$ which down-regulate monocyte surface marker expression, cytokine secretion, cytotoxicity and T-cell responsiveness. Gangliosides (GANGs) are components of human plasma with G_{M3} and G_{D3} being major constituents, and can bind to both plasma proteins and lipoproteins. The highest concentrations of GANGs are found in brain and mainly include G_{M1}, G_{D1a}, G_{D1b} and G_{I1b}. These are highly immunosuppressive by inhibiting T-cell proliferation, CD4 expression, generation of CTL and NK cell activity. In addition, GANGs may also suppress Ca^{2+} flux in T-cells (Ladisch *et al*, 1992; Zou *et al*, 1999; Dix *et al*, 1999).

3.2 The mechanism behind glioma immune evasion

Like any other tumors immune selective pressure on the glioma cells is also working to eradicate abnormal cells. Though the initial intensity is less and additional time is required to recognize and react, the precision is much higher against the neoplastic cells in brain (which will be discussed in the following sections). The genetic instability of glioma and

their repeated exposure to immune selection act as the key to develop glioma cell variants with enhanced capacity to evade immune defense.

Glioma cells are capable to secret copious factors that influence the immune system negatively. Cyclooxygenase enzyme COX-2 derived prostaglandin E2 (PGE2) bind with its receptor EPI-4 on glioma cells and encourage them to invade by increasing motility. PGE2 downregulate Th1 cytokines like IL-2, IFNγ and TNFα, and upregulate Th2 cytokines like IL-4, IL-10 and IL-6 (Wang & Dubois, 2006). Glioma cells secrete IL-10 which inhibit IL-2 induced T cell proliferation, DC and macrophage activation (Grutz, 2005). IL-10 is expressed by Treg cells present in glioma vicinity (Sakaguchi, 2005). TGFβ with its three isoform (TGFβ1,2,3) is involved in regulating inflammation, angiogenesis and proliferation (Govinden and Bhoola, 2003). TGFβ is the dominant isoform expressed by glioblastoma. They inhibit maturation of professional APCs, obstruct the synthesis of cytotoxic molecules including perforin, granzymes, FasL in activated CTL (Thomas and Massague, 2005). This cytokine may also efficiently recruit T reg cells in glioma. Glioma shows a considerable level of resistance against Fas induced apoptosis. Decoy receptor 3 (DcR3) is expressed in brain tumor and prevents Fas mediated apoptosis as well as decreases infiltration of CD4 and CD8 T cells (Roth *et al*, 2001). Apoptosis inhibitory proteins (IAPs) are active in glioma which inhibit caspase activity (Gomez & Kruse, 2006). Some of the glioma cells express FasL to counteract with the immunocytes (Husain *et al*, 1998).

As cell to cell contact plays an important role to deliver the immune assault, glioma cells take the strategy to minimize or impair these adhesions. Cell adhesion interaction between glioma and immune cells was found to be prevented by a thick glycosaminoglycan coating and protect the neoplastic cells from CTL action (Dick *et al*, 1983). In glioma condition, ICAM-1/LFA-1 interaction is interrupted which inhibit target cell lysis by tumor specific T and NK cells (Schiltz *et al*, 2002; Fiore *et al*, 2002). The aberrant HLA class I expression in glioma helps them to evade T cell detection of transformed cells and subsequent cytotoxicity (Rosenberg *et al*, 2003). In glioma, B7-H1 (B7-homologue 1, a costimulatory molecule) inhibits allogenic T cell activation and associated cytokine secretion (Wilmotte *et al*, 2005).

Some other factors like Indoleamine 2,3-dioxygenase (IDO) expression in glioma cells cause T cells to starve for tryptophan, cell cycle arrest and tolerance (Uyttenhove *et al*, 2003). Interestingly, IFNγ stimulate IDO production in glioma, create a local tryptophan shortage and T cell tolerance (Shirey *et al*, 2006). The activation of STAT-3 is another trick for glioma. STAT-3 regulates the anti-apoptotic proteins like Bcl-2, Bcl-XL, Mcl-1, cFLIP, surviving etc in glioma (Rahaman *et al*, 2005; Akasaki *et al*, 2006). Glioma uses various factors including chemokines and matrix degrading enzymes secreted from the brain macrophage/microglia population for their migration and spread in brain (these will be discussed later).

4. Undaunted immune effort continues to resist transformed cells

4.1 T cells mature to effector state after local interaction with APCs in CNS, even in brain tumor

The experimental evidences furnished by Ford and his colleagues in 1996 revealed that the resident antigen presenting cell of brain i.e., microglia, interacts with the T cells to induce final effector function (Ford *et al*, 1996). Years' later studies with GFP-labeled encephalitogenic T cells specific for MBP ($T_{MBP\text{-}GFP}$ cells) showed that, with the onset of the disease, huge number of CD4+ effector cells infiltrate in CNS with upregulated chemokine receptors. But these infiltrated $T_{MBP\text{-}GFP}$ cells when recovered after 24 hrs from brain

parenchyma or neuropil they showed fresh sign of reactivation with upregulation of OX-40 and IL-2R, and upregulated expression of IFNγ, TNFα, TGFβ, IL-2, IL-10, CD3 mRNA expression (Flugel *et al*, 2001). These observations suggested the importance of brain APC at the site of proper functioning of the recruited cells.

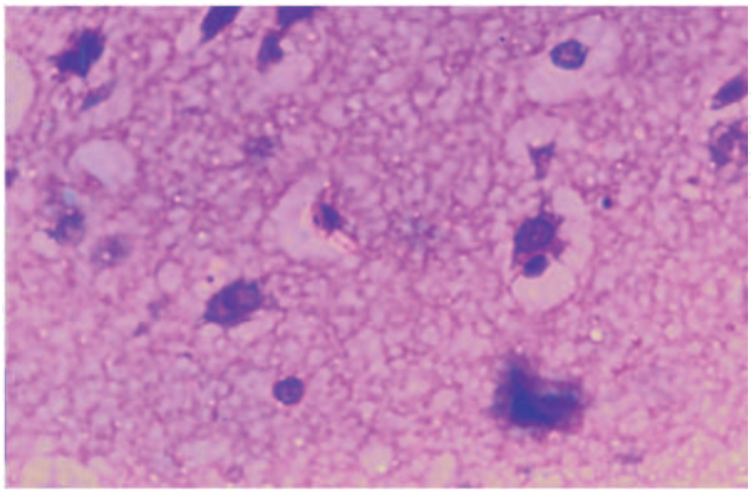

Fig. 3. The section shows that infiltrated lymphocytes in brain parenchyma interact with transformed oligodendroglial cells in a murine oligodendroglioma model and offer them the 'kiss of death'. One oligodendroglioma cell nucleus is protruded out of the cytoplasm and for the other cell, the lymphocyte is overlapping with it. One oligodendroglioma cell, one astrocyte and a free lymphocyte is visible in the field. (Magnification 1000X, oil immersion in Olympus CH20i Microscope and photographed by Olympus DSC)

The function of APC is now becoming more substantial in CNS as some new experimental evidences indicate that they are important to reshape and retain Ag-specific CTLs in the site of neuropathogenesis. In a series of experiments Walker and team addressed the issue with precision. Whether CNS retention of tumor specific MHC class I restricted $CD8^+$ T cells also require recognition of local APC cross-presenting tumor Ag was the problem under scrutiny. They used murine glioma transfected with cDNA encoding HLA-CW3 implanted in mice model. The observation was a massive expansion of $H2K^d/CW3_{170-179}$-specific CTL using BV10TCR after immunization with CW3. In that animal model the endogenous presentation was tactically avoided and due to the absence of MHC class II on MT-CW3 transfect, the CD4 arm is also avoided. Therefore any expansion of $H2K^d$ restricted CW3-specific CTL suggests the involvement of hosts APC at the tumor site. Detection of the localization of specific CTL, their cytotoxic efficacy and retention of effector functions in an antigen dependent manner speaks the importance of local APC within CNS (Calzascia *et al*, 2003). They are activated macrophage/microglia and cells with DC phenotype found infiltrated heavily in tumor. In subsequent studies they also provide support for the fact that T cell homing at the specific CNS tumor site is defined by the cross-presentating APCs there and not predetermined in the lymph nodes where initial priming occurs (Calzascia *et al*, 2005). In extended studies it was further found that Ag-experienced $CD8^+$ T cells further differentiate at the intracerebral tumor site with enhanced IFNγ and Granzyme-B expression and induction of $\alpha_E\beta_7$ integrin that facilitate their retention in brain (Masson *et al*, 2007). Thus cytotoxic activity of lymphocytes on glioma is not rare [Figure – 3].

4.2 Microglia, the local/resident APCs of brain accumulate in glioma

Microglia is designated as local or resident antigen presenting cell throughout the brain parenchyma or neuropil and its margin. Most emphatic efforts of microglial research in the last two decades were invested to explore its functional relevance in the brain tissue. The striking feature of microglia is its versatile ability to respond according to the CNS microenvironment. Functionally speaking, microglia is a hybrid between white blood cells and glial cells, which is intended to protect and support the neuronal environment in brain. Microglia can respond against an extensive list of biochemical factors ranging as diverse as glycoconjugates, neurotransmitters or cytokines/chemokines (Nakamura, 2002).

Nearly two decade of studies demonstrated the causative effects of chemokines in glioma microenvironment for macrophage/microglia infiltration. The C-C family chemokines, viz, monocyte chemotactic protein 1 (MCP-1) was first purified from glioma and Leung *et al*, 1997 found that with increased MCP-1 the macrophage/microglia infiltrates in glioma. Astrocytoma cells were found capable of producing MCP-1, and complementary receptor CCR2 was present and expressed on activated microglia (Leung *et al*, 1997). In 2003, evidence showed that, MCP-1 promoted the microglial migration in glioma and microglia infested glioma grew rapidly (Platten *et al*, 2003). The involvement of PI-3K/Akt pathway was assumed in the secretion of microglia derived factors that mediate glioma invasiveness (Joy *et al*, 2003; Pu *et al*, 2004). CSF-1 (colony stimulating factor 1), which acted as chemotactic and mitogenic factors for myeloid lineage cells, and its receptor, were long been detected in glioma, whereas microglia also possessed the option of secreting and receiving the factor from self and neighboring cells. Eventually from glioma G-CSF/GM-CSF (granulocytes and granulocytes macrophage colony stimulating factor) were secreted and influenced the differentiation and maturation process of microglia like other myeloid lineage cells. Badie *et al*, 1999, *in vitro* demonstrated the specific microglia attracting capacity of glioma by the hepatocyte growth factor/scatter factor (HGF/SF). HGF/SF signals the spectrum of mesenchymal cells for mitogenic stimulation, invasion and extravasation. Microglia possesses its receptor Met and can produce HGF/SF, whereas the glioma cells are capable of doing the same (Badie & Schartner, 2001). Thus, the balancing ratios of the factors in glioma microenvironment act as the determinant in the migration process of the cells.

In 2002, the 15.3 KDa heparin-binding peptide Pleiotrophin (PTN) was found to appear in adult human glioma, normally a mitogenic/angiogenic factor in embryonic stage. Uniquely, PTN did not help to proliferate the glioma cells by its own, rather influenced microglial accumulation by acting as strong chemotactic and mitogenic agent. Its action thus passively helped glioma growth by targeting endothelial and microglial cells (Mentlein & Held-Feindt, 2002). The question arose that what would be the interest of glioma to include microglia in its vicinity? In fact, the role of infiltrating macrophage/microglia in the process of angiogenesis in glioma was hinted previously when macrophage associated heme-oxygenase-1 (HO-1) enzyme was found to be correlated with the vascular density of human glioma (Nishie *et al* 1999). Another enzyme cyclooxygenase (COX)-2 was found to be produced in higher amount in microglia isolated from intracranial glioma which increased the prostaglandin E_2 (PGE_2) production. The study suggested that glioma infiltrating microglia contributed in developing fatal cerebral edema in glioma through COX-2 dependent pathway. It was reported that PGE_2 increased the permeability of vascular endothelium by cytoskeletal rearrangement where TNFα acted as positive inducer. In that case, microglia was the source of both COX-2 and TNFα probably playing a role in its own migration, leukocyte trafficking and in parallel, glioma invasiveness (Badie *et al*, 2003).

Contrary to the reports and assumptions, others demonstrated that TNF dependent action enhanced the macrophage/microglia recruitment in glioma where they form small cavities named microcysts and reduces the glioma growth (Villeneuve *et al*, 2005). A report stated that, the infiltrated macrophages ($CD11b^{+}CCR3^{-}CD45^{high}$) caused TNF induced apoptosis in GL261 glioma cells where related microglial cells ($CD11b^{+}CCR3^{+}CD45^{+}$) were negligible (Nakagawa *et al*, 2007). Actually the thin line of demarcation of cellular identity between macrophage and microglia could not exclude any of them from the function of TNF dependent glioma elimination. Opposing the recent believe of pro-tumoregenic role of macrophage population in different tumors, the reports raised question against application of anti-inflammatory drugs to suppress microglial action in glioma. To reestablish its role against glioma, the mechanism of their phagocytic recognition, killing machinery, and antigen presentation to CTL etc must have to be introspected more specifically.

4.3 Microglia protects host brain as well as support glioma: A bi-edged sword

Further findings showed that microglia helped glioma to invade by releasing matrix degrading enzymes. Even it was recently found that in rare Neurofibromatosis 1 (NF1), the heterozygote microglia had the role to promote glioma growth (Daginakatte & Gutmann, 2007). In 2005, it was found that metalloprotease-2 (MMP-2) activity was increased in microglia by the soluble factors released from glioma cells (Markovic *et al*, 2005). Thus glioma in turn influenced microglia to invade and migrate, which was utilized by neoplastic cells itself to spread and grow. Previously, a separate study hinted the process when the motility of GL261 mouse glioma cells was assessed in presence of microglia. Even the microglia stimulated with GM-CSF or LPS enhanced this migration (Bettinger *et al*, 2002). Adenosine mediated anti-inflammatory effects on macrophage cell lines by modulating the cytokine balance was observed. Additionally, macrophage and microglia both the cells were found to present adenosine receptors. In 2006, Synowtz and his team found the effect of nucleoside Adenosine on microglial cell and glioma. Deficiency of A1 adenosine receptor (A_1AR) on microglia helped to grow the GL261 glioblastoma cells and increased number of A_1AR expressing microglia in the site inhibited this growth. The mentioned study also hinted that adenosine signaling through the receptor depleted glioma influenced microglial MMP-2 release, which in turn restricted glioma growth and invasion (Synowitz *et al* 2006). Again, Kettenmann and colleagues observed that Microglia express membrane type 1 metalloprotease (MT1-MMP) in glioma condition, which helps to activate glioma released pro-MMP2 and thus promotes the spread of glioma in brain parenchyma (Markovic *et al*, 2009). Their most recent finding is that the antibiotic minocycline attenuates microglial MT1-MMP expression in glioma and as a result neoplastic cell expansion is reduced in glioma (Markovic *et al*, 2011).

Plasticity, its migration to the site of injury or inflammation, response and then departure from the site required a plausible explanation mostly for its movement. Microglia was found to express α6β1 integrin, which was the receptor for laminin expressed on the extracellular matrix constituent projections of astrocytes. This particular adhesion was for migration and under strict control of cytokine milieu (Milner & Campbell, 2002). It was found recently that another integrin α5β1 expressed both on glioma and microglial cells were capable of inhibiting glioma growth when attenuated. Remarkably it was found that, the attenuation process and resulting depletion of glioma required the presence of microglial cells (Färber *et al*, 2008). It might be probable that microglia secreting products had control over this integrin-laminin adhesion and migration of cell itself and invasive migration of glioma cells.

Regarding the cytokine microenvironment, the role of TGF-β was hinted in migration (Milner & Campbell, 2002). The specific importance of the cytokine was demonstrated by RNAi mediated gene silencing of TGF-β in promoting growth and invasiveness of glioma by integrin family adhesion molecule (Wesolowska *et al*, 2008). Recently it was found that cyclosporin A (CsA), an inhibitor of calcineurin and immunosuppressive in effect, could inhibit microglia mediated glioma invasion and cause to change morphological structure of microglia via MAPK signaling (Silwa *et al*, 2007).

In the present context, most of the studies demonstrated pro-tumerogenic action of microglia in glioma, which was facilitated by the secretary products, signaling molecules including cytokines, chemokines and receptors etc. In parallel, glioma cells favor microglial migration and encroachment in its vicinity. Though primarily macrophages/microglia are the cells to defend host tissue from faulty or malfunctioning cells or pathogens, their pro-glioma role leads to confusion. Remarkably, several findings also came with hopeful antagonistic results as already mentioned, where the roles of TNFα, TGFβ, A_1AR dependent MMP-2 inhibition etc were focused (Villeneuve *et al*, 2005; Nakagawa *et al*, 2007; Synowitz *et al* 2006; Wesolowska *et al*, 2008). In 2007, Galarneau and team demonstrated that macrophage/microglia depletion helped in glioma growth (Galarneau *et al*, 2007). The study hinted for a separate anti-tumor potential of the cells. These contradicting results present microglia with a double agent stature.

4.4 Glioma antigen presentation by microglia

To determine the antigen presenting role of microglia their MHC class II expression along with the co-stimulatory molecule like B7.1 (CD80) and B7.2 (CD86) had been evaluated. Badie and his team found the lower level of expression of these essential surface molecule for APC function in microglia freshly isolated from glioma invasive cells and that suggested suppressive effect on glioma microenvironment *in vivo* (Badie & Schartner, 2001). In a comparative study of different rodent glioma model viz., C6, 9L and RG2, the expression profile was found to vary significantly depending on the immunogenicity of the model. The costimulatory B7 molecule expression could be favored when microglia were rejuvenated by cytokines GM-CSF and IFN-γ *in vitro* (Badie *et al*, 2002). At the same time, Graeber with his colleagues scanned 97 glioma samples of different WHO grades and found no such simple relations of the MHC expression of the cell with tumor grades, rather found downregulation of MHC class II in tissue areas where dense glioblastoma cells were infested. According to them microglia were functional in astrocytic tumors, though might be subjected to suppression with T cell clonal anergy in that glioma microenvironment (Tran *et al*, 1998).

The stimulatory effect of the novel glycoprotein T11TS/SLFA-3 on microglial MHC class II expression was found. The dose-time dependent efficient MHC expression was found on microglia in rodent bearing experimental glioma when treated with T11TS (Begum *et al*, 2004). Chaudhuri and her team also identified another important costimulatory molecule CD2 on microglia, which could also be regulated by the glycoprotein dose in glioma condition (Begum *et al*, 2004; Chaudhuri & Ghosh, 2006). A separate study by her team found simultaneous co-expression of MHC class II and CD2 on microglia in glioma where both expressed in low quantity (Sarkar *et al*, 2004). This observation with others supported the view of immunosuppressive milieu offered to microglia in glioma mostly by TGFβ, IL-10, PGE_2, gangliosides etc (Zou *et al*, 1999; Graeber *et al*, 2002), which could also simultaneously cripple the infiltrated lymphocytes (Dix *et al*, 1999). In this regard, the fact that microglia was the source of that IL-10 in glioma, had been finally established by Wagner and team (Wagner *et al*, 1999).

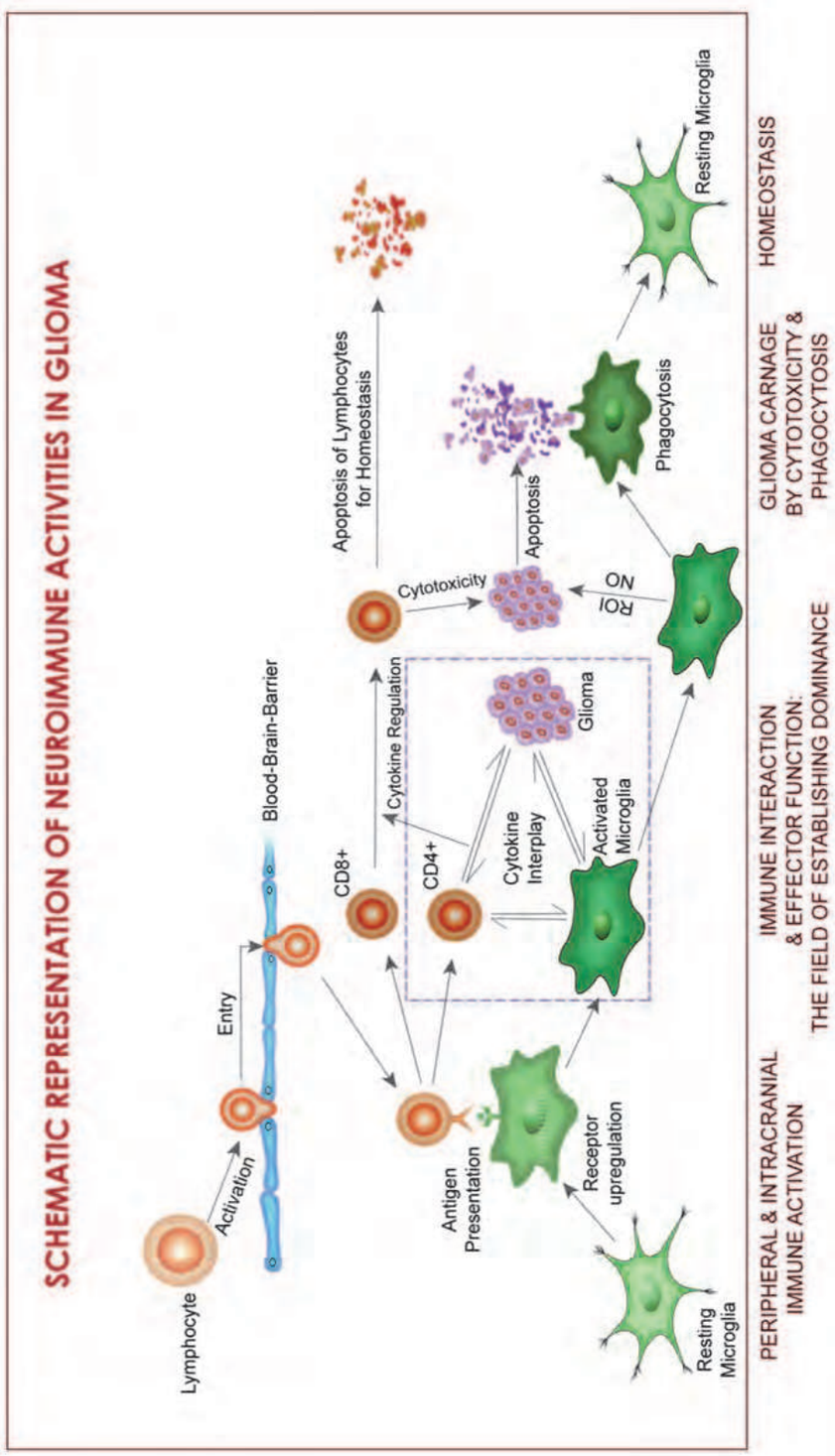

Fig. 4. This schematic diagram shows the activities of immune components in brain during glioma. After activated glioma antigen specific T cells enter into brain parenchyma they progressed towards glioma through parenchyma. Simultaneously, during glioma pathogenesis resident resting microglia get activated, upregulate their receptors, enhance

their local antigen presenting capacity and move towards glioma vicinity where astrocytic projections may assist this movement by providing the pavement for integrin-laminin interaction. At the glioma site, microglia locally represent antigens, produce cytokines and adhesion molecules to dialogue with lymphocytes which help them to mature and attain final effector function. At this point, a triangular complex interaction circuit become active between infiltrated lymphocytes, microglia and glioma cells when glioma tries to cripple the immune attack by applying many of its tricks (as discussed in the text). Overall cytokine, chemokine, growth factor and immunosuppressive factor become crucial to determine the success of immune defense or glioma. At the next step, cytotoxic T cells exert perforin, granzyme, FasL and other cytotoxic means to kill glioma and microglia uses its reactive oxygen and nitrogen intermediates to damage the abnormal or neoplastic cells. Target cells, intact, damaged or dead debris are scavenged by microglia. If the immune system manages to overcome the situation for a certain period they return to homeostasis. But aggressive glioma, after the initial arrest, overrules the immune defense by its rapid proliferation rate, immune evasion strategies and diverse modes for bypassing the attack. Gaining dominance during the triangular interaction phase marks the success of the party in the succeeding phases (Adopted from *Chaudhuri & Ghosh, 2006, CNSAMC*).

Hemiberger and colleagues studied the myeloid lineage cells in post-operative tissue samples in human glioma. Accepting the cellular identity crisis, these workers found macrophage/microglia and dendritic cell populations within the tumor tissue. In their higher grade glioma samples microglial population though found to express MHC class II, lacked co-stimulatory CD80, CD86 and CD40, crucial for T cell functioning. Activation of microglia via Toll-like receptors (TLRs) were also insignificant to augment tumoricidal activity (Hussain *et al*, 2006a). Particularly, proinflammatory cytokines including IL-1β, IL-6, TNF α could not be sufficiently released to launch substantial innate immune function against glioma, however their phagocytic function was not impaired and also exhibited low level of non-specific cytotoxicity (Hussain *et al*, 2006b). In rodent glioma model lack of proinflammatory cytokines IFN γ, IL-12 and IL-6, and conversely cumulative dominance of IL-4 and IL-10 favoring the suppression of immune response was recently observed (Ghosh *et al*, 2010). Microglial activity stature was also reflected in their morphometry in scanning electron microscopy (SEM), where their filapodial extensions, sizes and shapes had shown noticeable alterations (Begum *et al*, 2003).

4.5 Microglia can destroy glioma cells

The cytotoxic effector function is an important part of CNS microglia/macrophage population which mainly dependents on its phagocytic mode of action. For the purpose super oxide anion production is the major function of phagocytic cells, however microglia generate sufficient endogenous NO in addition (Beyer *et al*, 2000). When microglial effector function in rat glioma model was studied, it was found that microglia mostly depends on NO production than ROS generation for exerting effector activity, whereas peripheral macrophages mainly depends on ROS for their normal phagocytic functions (Ghosh *et al*, 2007). With tumoricidal actions NO plays certain role in complex signaling network of cytokine production, angiogenesis etc in brain microenvironment. Even microglia was found to release iNOS/NO from astrocytoma cells in contact. This was by IL-1β production of activated microglia and probably via p38 MAPK and NF-κB signaling pathway (Kim *et al*, 2006).

Expression of Fas ligand on a cell may cause damage to adjoining cells or infiltrated activated lymphocytes in the tissue by triggering the death pathway. In glioma, FasL expression was thought to be a means of immune escape, whereas, investigations found FasL expression also on microglial cells in glioma (Badie *et al*, 2001). Hence, it could be thought that microglia would play role in local immune suppression by limiting the lymphocyte populations; or it might express FasL to damage glioma cells, which in turn restricted or crippled the lymphocytes infiltrated locally. Microglia prefers to phagocytose the damaged cells rather than intact ones (Bohatschek *et al*, 2001). A study showed that after adoptive transfer of alloreactive cytotoxic T cells in rat 9L gliosarcoma infested brain, the CTL damaged glioma cells were removed by phagocytic scavenging activities of microglia, whereas undamaged ones were spared (Kulprathipanja & Kruse, 2004). In this process of either Fas or oxidative stress mediated cell death, externalization of phosphatidylserine was found to be crucial in corpse clearance by microglia. Experimental evidences revealed increasing PS externalization in correlation with cytotoxic effector functions of microglia and infiltrated lymphocytes. Additionally, the investigation showed that microglia population was more steady than infiltrated lymphocytes as Bcl-2 aided the cells to maintain that steady turnover rate and low apoptosis in brain microenvironment (Kagan *et al*, 2002 & Ghosh *et al*, 2007).

5. Conclusion: Future immuno-therapeutics must capitalize this resident and infiltrated immunocyte liaison to combat glioma

Now it can be clearly stated that lymphocytes can enter into the brain parenchyma. During their entry, they are checked by the antigen presenting cells for their glioma antigen specificity. APCs try to ensure this glioma specific T cell entry by restimulating the candidates presenting the glioma antigens mostly in perivascular space and allied blood brain interface (Engelherdt, 2010). After entering they migrate to glioma and again interact with the local APCs which help them to gain maturation and final effector function. In this process peripheral APC in brain and 'so called' resident microglia as well as DCs also play very important role. The role of local APC in glioma immunity has been detailed by Ghosh and Chaudhuri with a new outlook to explain the contradiction of glioma promoting role of microglia (Ghosh and Chaudhuri, 2010).These myeloid cell populations have the potential to act as chief immunomodulator in brain by surveillance in the tissue environment, guiding the leukocytes in CNS and simultaneously exerting effector function to neoplastic cells. The damaging activities of the cell are probably their own misfired 'goodness' or their potential that is misled by glioma cells. Thus, both the lymphocytes and local APC (predominantly microglia) are capable of exerting the immune effector function against glioma in spite of the immune-compromise in the brain and glioma immune evasion strategies [Figure – 4].

Now the success of immunotherapeutic approaches against glioma, largely as adjuvant therapeutic strategy, depends on the proper usages of this delicate immune defense against this detrimental threat. The battle becomes more interesting and challenging because the opponent is extremely clever. So development of immunotherapeutic strategies against glioma needs detailed and critical interpretation of the work-plan of immunity in glioma and its careful application. Basic findings are increasing the repertoire of information about immune activity deep into the brain during glioma which in turn provide us newer tactics or facilitate the amendment of old ones for better effects (Dietrich *et al*, 2010; Vauleon *et al*,

2010). Even some of the approaches interestingly propose microglia as an effective vehicle for gene therapy and drug delivery by using its predifferentiated cellular status (Neumann, 2006). Present immunotherapeutic advancements and limitations will be discussed in other chapters of this book and beyond the scope of this article. In this essay, the basic immune mechanisms, which are active in glioma, has been detailed. Further development of effective therapy needs this fundamental background knowledge for setting up a new immunotherapeutic intervention against glioma.

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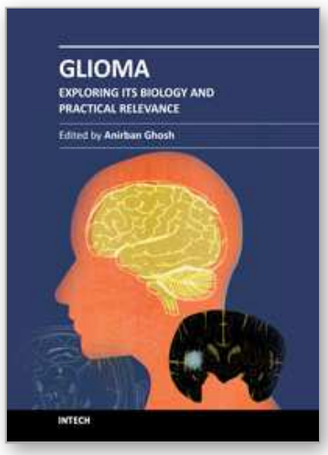

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The tittle 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

How to reference

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