

Genetic and Immunology of Brain Tumors

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1. Introduction

Tumors of the intracranial neoplasms are devastating because they frequently cause mortality or morbidity. Current studies have shown that the immune system and genetics may play a critical role in development of different kinds of brain tumors.

New insights into the causes and potential treatment of intracranial neoplasms have come from discovering connections with genes that control cell growth, differentiation and development of brain cancer. Host immune response is one of key points in protection against brain tumor development.

This section will outline what is known about molecular genetics, biology and immunogenetics of brain tumors.

- We will first focus on main oncogenes which are seen in CNS tumors and try to find answer how do tumor-brain interactions contribute to development of brain tumor.
- Finally we will discuss the mechanisms of immune activation and immune escape during an anti-tumor specific response, and new concepts for immunogenetic therapeutic intervention..

Thus, the data of immunogenetic pathways that are differentially involved in tumor initiation may represent a novel approach for the treatment of malignant brain tumors.

2. Genetic and immunology of brain tumors

Brain tumors are one of the leading cause of cancer mortality and remain difficult to cure despite advances in surgery and adjuvant therapy. Recent studies are focused on the molecular and cellular analysis of the bulk tumor mass. Glioma is the most common and mortal type of brain tumors (Kleihues et al., 2002). They are typically comprised of morphologically diverse cells that express a variety of neural lineage markers. Gliomas that share similar morphology and phenotype can have a very different prognosis and response to treatment. Alterations of multiple genes in the cell cycle and regulatory pathways plays an important role in tumorigenesis and causes to formation of subtypes (Singh et al., 2003). So researches in gene therapy have been often since 1912 because no effective therapy is achieved until now in spite of traditional treatments including surgery, radiation therapy, and chemotherapy (Culver et al., 1992). Formerly, the brain has been regarded as an immunologically privileged organ site because it possesses a distinct blood-brain barrier (BBB) and lacks discrete lymphatic structures (Yoffey & Courtice, 1970). Despite these factors minimizing central nervous system (CNS) immune function, a highly adapted system of immune surveillance presents, and effective immune responses can occur in the

CNS. Function of both the complement system (Bernheimer et al., 1988) and the antigen-antibody system, including functional B cells (Aloisi et al., 1999; Sandberg-Wollheim et al., 1986) have been found within the CNS. In the case of CNS pathologies resident antigen-presenting cells (APC) of the CNS, microglia cells, undergo activation and upregulate both major histocompatibility complex (MHC) and costimulatory molecules, and also contribute to both CD41 and CD81 specific T-cell responses (Aloisi et al., 1998; Brannan & Roberts, 2004; Hickey & Kimura, 1987; Hickey et al., 1991; Hickey, 2001; Krakowski & Owens, 2000). Actually a small number of lymphocytes are found in normal, healthy brain (Hickey & Kimura, 1987) however both resident lymphocytes and activated T cells have the capability to cross the BBB (Hickey & Kimura, 1987; Hickey et al., 1991; Hickey, 2001). Several lymphocytes also infiltrate the CNS in the presence of neoplasms (Han et al., 2010). Thus considering these factors new and more effective adjunctive treatments are needed.

3. Brain tumors and oncogenes

Oncogenes are functional mutations associated with cancer progression. They are derived from normal cellular genes called proto-oncogenes. The oncogenes that promote the tumor growth and development affecting mechanisms, such as cell proliferation, invasion, angiogenesis, and resistance to apoptosis by produced proteins are associated with the brain tumors. The protein synthesis which was gene product may increase or functional changes can be seen as a result of oncogenic mutation.

The oncogenic activation associated with nervous system tumors is in the form of gene amplification and the number of cell-specific gene increases. The most common oncogenic change is the amplification of the epidermal growth factor receptor (EGFR) gene and the mutations of the TP53 gene (Ekstrand et al., 1991; Libermann et al., 1985; Wong et al., 1987). The EGFR gene that is activated by growth factors such as EGF, TGF- α is "transmembrane tyrosine kinase" codes.

EGFR gene amplification was observed 40-50% of cases with glioblastoma multiforme, but it is rare in the anaplastic malignant astrocitoma (Brady et al., 1992; Ekstrand et al., 1991; Humphrey et al., 1990; Wong et al., 1987). This change is predictive for the malignancy degree of the astrocitomas (Ng & Lam, 1998). In malignant astrocitomas, the gene amplifications such as the MYCN, CDK4, MDM2, CCND1, and MET including the growth factors family of tyrosine kinase like EGFR were also determined (Bigner et al., 1987; Fischer et al., 1995; He et al., 1994; Reifenberger et al., 1994).

However, these amplifications were observed lesser than EGFR. In addition, the most common amplification was 10-15% CDK4 in malignant astrocitoma and glioblastoma. Each of these genes have been associated with the malignancy degree of glial tumors. The oncogenic changes were seen less than 10% in the other CNS tumors except for malignant astrocitomas. In medulloblastoma, the CMYC and MYCN amplifications were reported. Additionally, the β -catenin and TCF mutations were also detected in rare cases (Raffel et al., 1990; Wasson et al., 1990; Zurawel et al., 1998).

4. Gen therapy

'Gene therapy' can be defined as the transfer of genetic material into a patient's tumor cells by using stereotaxic injection. Up to present, various treatment strategies utilizing gene therapy have been used, including gene transfer for modulating the immune system,

enzyme prodrug ('suicide gene') therapy, oncolytic therapy, replacement/ therapeutic gene transfer, and antisense therapy (Bansal& Engelhard, 2000). Many of them have been attempted both experimentally and in clinical trials (Iwami et al., 2010; Licht et al., 1996; Lun et al., 2010; Pedersini et al., 2010; Schmidt et al., 2011; Steffens et al., 2004; Yawata et al., 2011). Mainly these approaches are based on previously established anti-neoplastic principles, like prodrug activating enzymes, inhibition of tumor neovascularization, and enhancement of the normally infirm anti-tumor immune response.

The strategies of gene therapy can be categorized as follows (Mut& Ziyal,2010).

1. Enzyme prodrug: enzyme prodrug ('suicide gene') therapy.
2. Oncolytic therapy, replacement.
3. Transfer of potentially therapeutic genes such as tumor supressor (eg p53)
4. Antisense therapy.
5. Kemoprotection: Approaches which use the multidrug-resistance gene to protect bone marrow from myelosuppression following chemotherapy. Chemoresistance genes especially P-glycoprotein, the product of the multidrug-resistance (*MDR1*) gene, plays a major role in clinical treatment failure.
6. Gene therapy for boosting the activity of the immune system againts tumor cells

Approaches	Administered Genes
Enzyme prodrug: enzyme prodrug ('suicide gene') therapy	Suicide genes
Immuno-gene therapy	Genes of antigens and cytokins
Peplasma therapy	Therapeutic genes
Kemoprotection therapy	Multi-drug resistance gene (<i>MDR</i>)
Antisense therapy	Antisense DNA
Oncolytic virus therapy	Oncolytic genes

Table 1. Current treatment strategies used in gene therapy. (Karaoglan &Turkmen,2010)

Immune gene therapy aims to enhance the T cell mediated immune response againts to brain neoplasms by using genetically modified T cell therapy, vaccination therapy and cytokine therapy (Iwami et al., 2010). Cytotoxic therapy is mainly consist of either delivering of gene or virus therapy (Aboody et al., 2008; Aghi & Chiocca, 2006; Candolfi et al., 2009; Kroeger et al., 2010; Lawler et al., 2006). The most common studied conditional cytotoxic transgene is Herpes Simplex Type 1 thymidine kinase (TK), which converts the prodrug ganciclovir (or valacyclovir) into the highly toxic deoxyguanosine triphosphate causing early chain termination of nascent DNA strands (Beltinger et al., 1999). The bystander effect of the TK approach is related to the passage of phosphorylated ganciclovir to neighboring cells through gap junctions, amplifying the cytotoxic effect of TK gene therapy (Mesnil & Yamasaki, 2000).

4.1 Vectors in gene therapy

Several viral and non-viral vectors have been engineered and used for gene transfer, both experimentally and clinically.

Virotherapy is defined delivery of conditionally replicating viral vectors that solely replicate in tumor cells and kill them (Ferguson et al., 2010; Jiang et al., 2009; Markert et al., 2009). Viruses used for glioma gene therapy can be classified into 2 categories: replication-

incompetent viruses. In the first one, the vector is derived from a virus from which all or most of its genome has been removed, so minimizing the toxicity and retaining the gene delivery efficiency. In the second, only select viral genes are deleted or mutated so that viruses can replicate in and lyse tumor cells selectively (i.e., oncolytic viral therapy) (Iwami et al., 2010).

4.1.1 Strategies in transgenic viruses (Iwami et al., 2010; Kozarsky & Wilson, 1993; Markert et al., 2009)

1. Scientists add healthy functioning genes to cells that have damage or missing genes in order to substitute the bad non-working copy of the gene with a better copy of the working gene. The extraction of reproductive are of virus was done initially. Genes have been added to and removed from the viruses so they cannot replicate on their own, but they can still break out of the tumor cells and invade nearby dividing cancer cells.
2. Injecting of the tumor cell with genes that can kill the tumor cells. For instance, suicide genes are inserted into the tumor cells. A pro-drug or an inactive form of a toxic drug is administered to the patients, and this drug will kill off any tumor cells with the suicide genes in them. This method is called enzyme prodrug ('suicide gene') therapy, Once inside the tumor cells, the viruses produce an enzyme that will turn an otherwise harmless drug into one that is toxic to the tumor cells. When the patient is treated with the drug gancyclovir, the enzyme converts it into something that is toxic to the tumor cells, and those cells die.
3. Researchers can also transfer genetic materials into cancer cells by using ex-vivo techniques. Cancer cells are taken out of the body from the patient's blood or bone marrow surgically, and the necessary genes are added to them in the laboratory.
4. Other method that is commonly used in laboratory is the in-vivo techniques. Virus or a plasmid is entirely necessary because gene cannot be directly inserted into a cell. The gene is inserted into the host's cell by using a vector. A vector acts as a bacteriophage or a plasmid (circular, small pieces of DNA) that can transfer genes from one cell to another. Vectors from the viruses adenoviruses are often used for gene therapy because viruses reproduce by inserting their genetic material into the cells they infect.

Other transferring therapeutic genes to brain tumor cells are mostly used by HSV, retrovirus and adenovirus due to following key points. Application of adenovirus mediated gene therapy was successful in liver cell and respiratory epithelium (Kozarsky & Wilson, 1993; Kramm et al., 1995). Herpes simplex virus-thymidine kinase (HSV-tk) gene, had a good tendency to neuronal cells. Retroviral vectors have long survive in target cells (Kramm et al., 1995). Oncolytic reovirus and measles viral vectors are under development for GBM virotherapy (Kroeger et al., 2010).

Gene directed prodrug therapy utilizing the herpes simplex virus thymidine kinase gene was the first gene therapy experienced clinically (Mesnil & Yamasaki, 2000; Yawata et al., 2011). The most frequent used paradigm is based on the activation of ganciclovir to a cytotoxic compound by a viral enzyme, thymidine kinase, which is expressed by tumor cells, after the gene has been introduced by a retroviral vector. This paradigm has proven to be a potent therapy with minimal side effects in several rodent brain tumor models, and has proceeded to phase 1 clinical trials (Kramm et al., 1995).

Oncolytic viral therapy: This approach uses replication-competent viruses infect and lyse the target cells. An oncolytic vector should conditionally replicate within the target tumor

cells with minimal toxicity to the surrounding normal brain tissue. Oncolytic vectors are grouped as either mesogenic (moderately pathogenic, capable of producing viable progeny and infecting adjacent cells) or lentogenic (attenuated non-pathogenic, produces defective progeny and is incapable of spreading between tissues) (Dey et al., 2010). Replicating, oncolytic viruses have been developed from several species of viruses. The most common vectors are replicating herpes simplex virus (HSV), adenovirus and replication-competent retrovirus (RCR). Replicating herpes simplex virus (HSV) vectors have been tested for the treatment of malignant glioma (Grandi et al., 2009; Granelli-Piperno et al., 2000; Parker et al., 2009). The common widely studied oncolytic HSV vector is G207, a genetically engineered HSV-1 (Markert et al., 2000).

Tumor suppressor gene therapy: Mutation or inactivation of the *p53* tumor suppressor gene is one of the early genetic alterations in the tumor progression of gliomas (Fults et al., 1992; von Deimling et al., 1992). Using a gene to encode a tumor-suppressor protein in glioma cells that is mutated or absent. Is the fundamental of this approach? TP53 is most common studied suppressor gene, whose mutations have been reported in 30-60% of malignant gliomas (Louis et al., 2001; Vousden & Lane, 2007). It is demonstrated that the replacement of wild-type *p53* in tumor cells induced rapid cell death even in cells with the intact functional gene (Li et al., 1999; Roth, 2006).

Antisense therapy: Antisense oligonucleotides are single strands of DNA or RNA that are complementary to a chosen sequence. Antisense oligonucleotides specific for insulin-like growth factor-1 (IGF-1) or transforming growth factor b2 (TGF-b2) have been used in various clinical studies (Tambuyzer et al., 2009; Vauleon et al., 2010).

5. Non-viral methods

Non-viral methods provide certain advantages over viral methods, such as simple large scale production and low host immunogenicity, however small levels of transfection and expression of the gene are a disadvantage of this methods (Iwami et al., 2010).

1. Injection of naked DNA or naked PCR product,
2. Physical methods to enhance delivery
 - a. Electroporation
 - b. Gene gun
 - c. Sonoporation
 - d. Magnetofection
3. Chemical methods to enhance delivery

Synthetic oligonucleotides, lipoplexes and polyplexes, dendrimers

- a. Hybrid methods: Combination of two or more techniques. For example virosomes are combine with liposomes using an inactivated HIV or influenza virus.

Difficulties in gene therapy in brain tumors can be arranged as follows: (Mut & Ziyal, 2010).

1. Difficulties to recognize tumor cells as target for attack.
2. In order to inject gene cells into the specific region of the brain, to perform stereotactic brain surgery is mandatory.
3. After the genes are injected into the region, there is the possibility that the viral vectors that are used to transfer the genetic material into the cell might infect healthy cells as well as brain tumors.

4. The new gene might also insert into the wrong location in the DNA, thus leading to harmful mutations of the DNA and triggering unwanted reaction by the immune system.
5. The transferred genes can also be overexpressed by producing a lot of missing proteins.
6. Finally, inflammation of the lining of the brain or infection can occur after the treatment.
7. The negative side, on the other hand, is that the gene therapy will affect the development of the fetus in many unexpected ways like causing long-term illness or other side effects. The human gene pool can also be permanently affected by these gene alterations.

6. Suppressive factors of gliomas on immune system

Gliomas can abtain immune system at different steps of antigen recognition and immune activation (Parney et al., 2000). Many glioma cells express low or defective levels of human leukocyte antigens (HLA) and also ave been found deficient in proper antigen presentation for cytotoxic and helper T-cell activation (Flügel et al., 1999). Inhibition of antigen presentation by microglia and macrophages in the tumor micro environment also causes to the tumors' ability to escape immune detection.

In gliomas, T cells, specifically the CD41 population, both in peripheral blood and in the tumor microenvironment, have depressed function (Roszman & Brooks, 1985; Roszman et al., 1985). Innate helper T cells (CD41) reveal weak proliferative responses and dramatically lowered synthesis of the TH1 cytokine IL-2 (Das et al., 2008).

One hypothesis suggested that these are actually resident T cells passively infiltrating the tumor across a compromised BBB caused by the tumor; alternatively, they may represent a population that once was active but has been subsequently rendered inactive by the host of immunosuppressive mechanisms found in the tumor microenvironment (Han et al., 2010).

Secretion of various immune inhibitory cytokines and molecules by glioma cells also plays an important role in glioma-associated immunosuppression. High levels of expression of TGF- β 2, IL-10 and prostaglandin E2 are present in malignant gliomas (Couldwell et al., 1992; Nitta et al., 1994). TGF- β 2 mRNA is found in samples of glioblastome multiforme (GBM) (Bodmer et al., 1989).

Iatrogenic factors may also cause a systemic immunosuppression in patients with glioma (Roszman & Brooks, 1985). Corticosteroids given in the treatment of tumor-associated edema may cause inhibition of cytokine production and sequestration of CD41 T cells (Barshes et al., 2004). Otherwise recent reports suggest, however, that at therapeutic doses corticosteroids may not interfere with immunotherapy (Fenstermaker & Ciesielski, 2004; Lesniak et al., 2004).

Stimulation of microglia in the existence of tumor cells reduces the secretion of proinflammatory cytokines, such as tumor necrosis factor (TNF)- α , however also increases the secretion of the inhibitory cytokine interleukin (IL)-10 (Dix et al., 1999).

7. Immunotherapy

Immunotherapy is one of the new promising therapeutic approaches that can especially target tumour cells. Adoptive and active immunotherapies using lymphokine-activated killer cells, cytotoxic T cells, tumour-infiltrating lymphocytes, autologous tumour cells, and dendritic cells are mainly used in this approach (Prasad et al., 2004).

Microglial cells constitute the first step of defense for the brain. They migrate toward inflammatory zones and, after activation, possess phagocytic properties and synthesize several types of cytokines and chemokines (Tsurushima et al., 1999). They express a number of macrophage-associated markers and major histocompatibility (MHC) antigens suggesting that they may actually function as APCs in the brain thus evidence suggests that antigen presentation cells (APCs) are indeed present in the brain (Cash & Rott, 1994).

To date, it was generally suggested that immune reactions do not occur in the brain because of the blood-brain barrier (BBB) and the specific features of the brain such as the absence of conventional lymphatic vessels or the low level of circulating T cells. This hypothesis is not true exactly. Cell based immunotherapies are effective in brain tumors. Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells (NK Cell), cytotoxic T lymphocytes (CTL), etc., work together to defend the body against tumor by targeting abnormal antigens expressed on the surface of the tumor due to mutation. An adaptive immune response implies antigen recognition (Prasad et al., 2004). A variety of immunologically based strategies, including passive immunization and adoptive cellular immunotherapy (Fujimiya et al., 1999; Inoue et al., 1996; Kruse et al., 1990; Merchant et al., 1997; Plautz et al., 1997; Plautz et al., 1998) local and systemic delivery of biological response modifiers (Dranoff et al., 1993; Färkkilä et al., 1994; Jean et al., 1998; Jean et al., 2004; Lichtor et al., 1995; Ohno et al., 2009; Thompson et al., 1996; Yu et al., 1993) and vaccination with parental and genetically modified tumor cells (Dranoff et al., 1993; Jean et al., 1998; Lichtor et al., 1995; Thompson et al., 1996; Ohno et al., 2009; Yu et al., 1993) have been attempted.

7.1 Cytokine therapy

Cytokines are a heterogeneous group of soluble small polypeptides or glycoproteins, which have either pro- or anti-inflammatory activity and immunosuppressive activity, depending on the microenvironments. The tumor microenvironment consists of a variable combination of tumor cells, endothelial cells and infiltrating leukocytes, such as macrophages, T-lymphocytes, natural killer (NK) cells, B-cells and antigen-presenting cells (APCs). Cytokine production acts as a means of communication in the tumor microenvironment (Giezeman-Smits et al., 2000). Several strategies for delivery of cytokines to the CNS have been studied, including injection/infusion of recombinant cytokines, vectors containing cytokine encoding genes, cells that secrete cytokines, or cytokines linked to toxins (Das et al., 2008).

7.2 Passive immunotherapy

Passive immunotherapy includes serotherapy and adoptive immunotherapy. Serotherapy uses monoclonal antibodies to effect an antitumor response or to achieve very specific delivery of toxins, chemotherapy, or radiotherapy to the tumor cells. An important finding of its advantage is the identification of "tumor antigens," specific antigens expressed on tumor cell surfaces but not on normal brain parenchyma (Ohno et al., 2009). Targeted glioma antigens have included tenascin, EGFR and its mutated form EGFRvIII, chondroitin sulfate, vascular endothelial growth factor (VEGF) receptor, neural cell adhesion molecule (NCAM), and hepatocyte growth factor/scatter factor (Hopkins et al., 1996).

In adoptive immunotherapy, immune cells activated *ex vivo* are administered to the tumour-bearing patient. The activated cells are either injected directly into the tumour cavity or intravenously (Han et al., 2010). The first types of cells used for gliomas were

lymphocyte-activated killer (LAK) cells (Tsuboi et al., 2003). Cytotoxic T lymphocytes (CTL) can also be used. Autologous tumour cells (ATC) are generally used as antigen source (Holladay et al., 1996; Tsuboi et al., 2003). Another approach was to collect lymphocytes from lymph nodes (Holladay et al., 1996; Plautz et al., 1998; Plautz et al., 2000; Sloan et al., 2000; Wood et al., 2000).

Active immunotherapy involves strengthening patients' immunity in vivo by vaccination against tumor antigen. Tumor vaccines for malignant glioma have been the focus of great interest currently. Successful development of glioma vaccines, however, requires proper presentation of tumor antigens and induction of effective, durable antigen-specific T cell immune response. A lot of antigen sources can be used for active immunotherapy such as intact tumour cells, tumour protein lysates, tumour-derived mRNA, peptides eluted from tumour MHC class I molecules, and synthetic peptides (Ishikawa et al., 2007; Okada et al., 2007; Sloan et al., 2000; Steiner et al., 2004).

8. Conclusion

As brain tumor neoplasms constitute a formidable therapeutic challenge, gene and immunotherapy present powerful, novel opportunities for developing adjuvant therapies in brain cancer. However, more effective researches for adjuvant treatments of malignant gliomas are needed.

9. References

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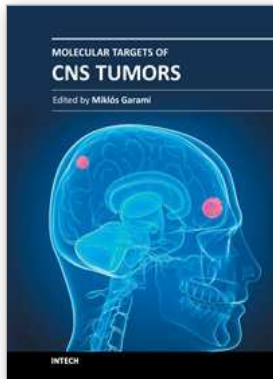
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